

2

Global Warming and Actinide Dependent Shadow Biosphere of Archaea and Viroids in Chronic Bone and Joint Disease

Introduction

Endomyocardial Fibrosis along with the root wilt disease of coconut is endemic to Kerala with its radioactive actinide beach sands. Actinides like rutile, endogenous digoxin as well as organisms like phytoplasmas and viroids have been implicated in the etiology of these diseases.¹⁻⁴ Endogenous digoxin has been related to the pathogenesis of degenerative bone and joint disease like spondylosis and osteoarthritis as well as postmenopausal osteoporosis.⁴ The possibility of endogenous digoxin synthesis by actinide based primitive organism like archaea with a mevalonate pathway and cholesterol catabolism was considered.⁵⁻⁸ An actinide dependent shadow biosphere of archaea and viroids in the above mentioned disease states is described.^{7,9} Metal actinides in beach sands have been postulated to play a role in abiogenesis.⁷ A hypothesis of cholesterol as the primal prebiotic molecule synthesized on actinide surfaces with all other biomolecules arising from it and a self replicating cholesterol lipid organism as the initial life form is presented.

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 K_m 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 NF κ B. 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 bone and joint disease.

Materials and Methods

The following groups were included in the study:- Degenerative bone and joint disease like spondylosis and osteoarthritis as well as postmenopausal osteoporosis. The study also included normal population with right hemispheric dominance and left hemispheric dominance. There were 10 patients in each group and each patient had an age and sex matched healthy control selected randomly from the general population. The blood samples were drawn in the fasting state before treatment was initiated. Plasma from fasting heparinised blood was used and the experimental protocol was as follows (I) Plasma+phosphate buffered saline, (II) same as I+cholesterol substrate, (III) same as II+rutile 0.1 mg/ml, (IV) same as II+ciprofloxacin and doxycycline each in a concentration of 1 mg/ml. Cholesterol substrate was prepared as described by Richmond.¹⁰ Aliquots were withdrawn at zero time immediately after mixing and after incubation at 37 °C for 1 hour. The following estimations were carried out: Cytochrome F420, free RNA, free DNA, polycyclic aromatic hydrocarbon, hydrogen peroxide, dopamine, serotonin, pyruvate, ammonia, glutamate, cytochrome C, hexokinase, ATP synthase, HMG CoA reductase, digoxin and bile acids.¹¹⁻¹³ Cytochrome F420 was estimated fluorimetrically (excitation wavelength 420 nm and emission

wavelength 520 nm). Polycyclic aromatic hydrocarbon was estimated by measuring hydrogen peroxide liberated by using glucose reagent. Informed consent of the subjects and the approval of the ethics committee were obtained for the study. The statistical analysis was done by ANOVA.

Results

Plasma of control subjects showed increased levels of the above mentioned parameters with after incubation for 1 hour and addition of cholesterol substrate resulted in still further significant increase in these parameters. The plasma of patients showed similar results but the extent of increase was more. The addition of antibiotics to the control plasma caused a decrease in all the parameters while addition of rutila increased their levels. The addition of antibiotics to the patient's plasma caused a decrease in all the parameters while addition of rutila increased their levels but the extent of change was more in patient's sera as compared to controls. The results are expressed in tables 1-7 as percentage change in the parameters after 1 hour incubation as compared to the values at zero time. The archaeal cholesterol catabolites and various parameters were upregulated in right hemispheric dominance, osteoarthritis and spondylosis. The archaeal cholesterol catabolites and various parameters were downregulated in left hemispheric dominance and osteoporosis.

Table 1. *Effect of rutile and antibiotics on free DNA and RNA.*

Group	DNA % change (Increase with Rutile)		DNA % change (Decrease with antibiotics)		RNA % change (Increase with Rutile)		RNA % change (Decrease with antibiotics)	
	Mean	±SD	Mean	±SD	Mean	±SD	Mean	±SD
LHD	4.37	0.15	18.39	0.38	4.37	0.13	18.38	0.48
RHD	22.99	1.56	65.19	4.10	23.27	1.36	65.66	3.93
Osteoporosis	2.26	0.25	7.45	0.40	2.30	0.12	7.62	0.30
Osteoarthritis	22.56	2.46	62.70	4.53	23.32	1.74	65.67	4.16
Spondylosis	23.30	1.42	65.07	4.95	23.11	1.52	66.68	3.97
F value	337.577		356.621		427.828		654.453	
P value	< 0.001		< 0.001		< 0.001		< 0.001	

Table 2. *Effect of rutile and antibiotics on cyt F 420 and muramic acid.*

Group	CYT F420 % change (Increase with Rutile)		CYT F420 % change (Decrease with antibiotics)		Muramic acid % change (Increase with Rutile)		Muramic acid % change (Decrease with antibiotics)	
	Mean	±SD	Mean	±SD	Mean	±SD	Mean	±SD
LHD	4.48	0.15	18.24	0.66	4.34	0.15	18.24	0.37
RHD	11.35	0.64	60.49	6.22	22.68	1.99	63.29	5.93
Osteoporosis	2.13	0.13	5.37	1.47	2.26	0.25	7.45	0.40
Osteoarthritis	22.29	1.66	59.02	7.50	23.23	1.97	65.89	5.05
Spondylosis	22.06	1.61	57.81	6.04	23.46	1.91	61.56	4.61
F value	306.749		130.054		348.867		364.999	
P value	< 0.001		< 0.001		< 0.001		< 0.001	

Table 3. *Effect of rutile and antibiotics on HMG CoA reductase and PAH.*

Group	HMG CoA R % change (Increase with Rutile)		HMG CoA R % change (Decrease with antibiotics)		PAH % change (Increase with Rutile)		PAH % change (Decrease with antibiotics)	
	Mean	±SD	Mean	±SD	Mean	±SD	Mean	±SD
LHD	4.30	0.20	18.35	0.35	4.45	0.14	18.25	0.72
RHD	21.06	2.32	63.87	6.22	21.00	2.54	57.42	7.07
Osteoporosis	2.33	0.17	7.24	0.59	2.25	0.17	7.01	0.65
Osteoarthritis	22.86	2.58	66.53	5.59	23.15	1.62	66.48	4.17
Spondylosis	22.38	2.38	60.65	5.27	23.00	1.64	66.67	4.21
F value	319.332		199.553		391.318		257.996	
P value	< 0.001		< 0.001		< 0.001		< 0.001	

Table 4. *Effect of rutile and antibiotics on digoxin and bile acids.*

Group	Digoxin (ng/ml) (Increase with Rutile)		Digoxin (ng/ml) (Decrease with antibiotics)		Bile Acids % change (Increase with Rutile)		Bile Acids % change (Decrease with antibiotics)	
	Mean	±SD	Mean	±SD	Mean	±SD	Mean	±SD
LHD	0.11	0.00	0.054	0.003	4.29	0.18	18.15	0.58
RHD	0.55	0.10	0.248	0.058	21.10	2.43	54.82	8.28
Osteoporosis	0.07	0.01	0.026	0.004	2.25	0.19	7.25	0.66
Osteoarthritis	0.56	0.05	0.220	0.052	22.29	1.47	64.35	5.58
Spondylosis	0.53	0.06	0.212	0.045	23.30	1.88	62.49	7.26
F value	135.116		71.706		290.441		203.651	
P value	< 0.001		< 0.001		< 0.001		< 0.001	

Table 5. *Effect of rutile and antibiotics on pyruvate and hexokinase.*

Group	Pyruvate % change (Increase with Rutile)		Pyruvate % change (Decrease with antibiotics)		Hexokinase % change (Increase with Rutile)		Hexokinase % change (Decrease with antibiotics)	
	Mean	±SD	Mean	±SD	Mean	±SD	Mean	±SD
LHD	4.34	0.21	18.43	0.82	4.21	0.16	18.56	0.76
RHD	11.12	0.66	59.68	6.24	23.27	1.68	67.35	3.77
Osteoporosis	2.16	0.18	5.91	1.38	2.24	0.17	6.29	1.06
Osteoarthritis	21.21	2.36	58.73	8.10	21.11	2.25	64.20	5.38
Spondylosis	21.07	1.79	63.90	7.13	22.47	2.17	65.97	4.62
F value	321.255		115.242		292.065		317.966	
P value	< 0.001		< 0.001		< 0.001		< 0.001	

Table 6. *Effect of rutile and antibiotics on ATP synthase and hydrogen peroxide.*

Group	ATP synthase % change (Increase with Rutile)		ATP synthase % change (Decrease with antibiotics)		H ₂ O ₂ % change (Increase with Rutile)		H ₂ O ₂ % change (Decrease with antibiotics)	
	Mean	±SD	Mean	±SD	Mean	±SD	Mean	±SD
LHD	4.40	0.11	18.78	0.11	4.43	0.19	18.13	0.63
RHD	11.99	0.38	66.34	3.39	17.60	3.53	54.68	5.09
Osteoporosis	2.30	0.12	7.62	0.30	2.24	0.23	5.36	0.99
Osteoarthritis	23.45	1.79	66.32	3.63	23.32	1.71	63.15	7.62
Spondylosis	23.17	1.88	68.53	2.65	22.86	1.91	63.66	6.88
F value	449.503		673.081		380.721		171.228	
P value	< 0.001		< 0.001		< 0.001		< 0.001	

Table 7. *Effect of rutile and antibiotics on delta amino levulinic acid and dopamine.*

Group	ALA % (Increase with Rutile)		ALA % (Decrease with antibiotics)		DOPAMINE % change (Increase with Rutile)		DOPAMINE % change (Decrease with antibiotics)	
	Mean	±SD	Mean	±SD	Mean	±SD	Mean	±SD
LHD	4.40	0.10	18.48	0.39	4.41	0.15	18.63	0.12
RHD	22.98	2.06	66.10	4.03	11.36	0.58	65.41	4.83
Osteoporosis	2.13	0.11	7.62	0.32	2.13	0.11	7.62	0.32
Osteoarthritis	23.45	1.79	66.32	3.63	23.43	1.57	66.30	3.57
Spondylosis	23.17	1.88	68.53	2.65	23.70	1.75	68.06	3.52
F value	372.716		556.411		403.394		680.284	
P value	< 0.001		< 0.001		< 0.001		< 0.001	

Abbreviation

BHD: Bihemispheric dominance

RHD: Right hemispheric dominance

LHD: Left hemispheric dominance

Discussion

There was increase in cytochrome F420 indicating archaeal growth in spondylosis and osteoarthritis as well as a decrease in growth in osteoporosis. The archaea can synthesize and use cholesterol as a carbon and energy source.^{6, 14} The archaeal origin of the enzyme activities was indicated by antibiotic induced suppression. The study indicates the presence of actinide based archaea with an alternate actinide based enzymes or metalloenzymes in the system as indicated by rutile induced increase in enzyme activities.¹⁵ There was also an increase in archaeal HMG CoA reductase activity indicating increased cholesterol synthesis by the archaeal mevalonate pathway. The archaeal beta hydroxyl steroid dehydrogenase activity indicating digoxin synthesis and archaeal cholesterol hydroxylase activity indicating bile acid synthesis were increased.⁸ The archaeal cholesterol oxidase activity was increased resulting in generation of pyruvate

and hydrogen peroxide.¹⁴ The pyruvate gets converted to glutamate and ammonia by the GABA shunt pathway. The archaeal aromatization of cholesterol generating PAH, serotonin and dopamine was also detected.¹⁶ The archaeal glycolytic hexokinase activity and archaeal extracellular ATP synthase activity were increased. The archaea can undergo magnetite and calcium carbonate mineralization and can exist as calcified nanoforms.¹⁷ There was an increase in free RNA indicating self replicating RNA viroids and free DNA indicating generation of viroid complementary DNA strands by archaeal reverse transcriptase activity. The actinides modulate RNA folding and catalyse its ribozymal action. Digoxin can cut and paste the viroidal strands by modulating RNA splicing generating RNA viroidal diversity. The viroids are evolutionarily escaped archaeal group I introns which have retrotransposition and self splicing qualities.¹⁸ Archaeal pyruvate can produce histone deacetylase inhibition resulting in endogenous retroviral (HERV) reverse transcriptase and integrase expression. This can integrate the RNA viroidal complementary DNA into the noncoding region of eukaryotic noncoding DNA using HERV integrase as has been described for borna and ebola viruses.¹⁹ The noncoding DNA is lengthened by integrating RNA viroidal complementary DNA with the integration going on as a continuing event. The archaea genome can also get integrated into human genome using integrase as has been described for trypanosomes.²⁰ The integrated viroids and archaea can undergo vertical transmission and can exist as genomic parasites.^{19, 20} This increases the length and alters the grammar of the noncoding region producing memes or memory of acquired characters as well as eukaryotic speciation and individuality.²¹ The viroidal complementary DNA can function as jumping genes producing a dynamic genome important in storage of synaptic information, HLA gene expression and developmental gene expression. The RNA viroids can regulate mRNA function by RNA interference.¹⁸ The phenomena of RNA interference

can modulate T-cell and B-cell function, insulin signaling lipid metabolism, cell growth and differentiation, apoptosis, neuronal transmission and euchromatin / heterochromatin expression. More of extensive archaeal integration into the human genome consequent to global warming can lead to spondylosis and osteoarthritis. Less of archaeal integration into the genome can lead to osteoporosis.

The archaea and viroids can regulate the nervous system including the NMDA / GABA thalamo-cortico-thalamic pathway mediating conscious perception.^{4, 22} NMDA / GABA receptors can be modulated by digoxin induced calcium oscillations resulting NMDA / GAD activity induction, PAH increasing NMDA activity and inducing GAD as well as viroid induced RNA interference.⁴ The cholesterol ring oxidase generated pyruvate can be converted by the GABA shunt pathway to glutamate and GABA. The dipolar PAH and archaeal magnetite in the setting of digoxin induced sodium potassium ATPase inhibition can produce a pumped phonon system mediated Frohlich model superconducting state²² inducing quantal perception with nanoarchaeal sensed gravity producing the orchestrated reduction of the quantal possibilities to the macroscopic world.^{4, 22} The archaea can regulate limbic lobe transmission with archaeal cholesterol aromatase / ring oxidase generated norepinephrine, dopamine, serotonin and acetyl choline.¹⁶ The higher degree of integration of the archaea into the genome produces increased digoxin synthesis producing right hemispheric dominance and lesser degree producing left hemispheric dominance.⁴ The increased integration of archaea into the neuronal genome can produce increased cholesterol oxidase and aromatase mediated monoamine and NMDA transmission producing right hemispheric dominant state. The left hemispheric dominant state is produced by less of archaeal integration into the genome. Right hemispheric dominance leads to osteoarthritis and spondylosis. Left hemispheric dominance leads to osteoporosis.²⁹⁻³⁶

Archaea and RNA viroid can bind the TLR receptor induce NF κ B producing immune activation and cytokine TNF alpha secretion. The archaeal DXP and mevalonate pathway metabolites can bind $\gamma\delta$ TCR and digoxin induced calcium signaling can activate NF κ B producing chronic immune activation.^{4, 23} The archaea and viroid induced chronic immune activation and generation of superantigens can lead on to spondylosis and osteoarthritis. Archaea, viroids and digoxin can induce the host AKT PI3K, AMPK, HIF alpha and NF κ B producing the Warburg phenotype.²⁴ The increased glycolytic hexokinase activity, decrease in blood ATP, leakage of cytochrome C, increase in serum pyruvate and decrease in acetyl CoA indicates the generation of the Warburg phenotype. There is induction of glycolysis, inhibition of PDH activity and mitochondrial dysfunction. The archaea and viroid generated cytokines can lead to TNF alpha induced immune activation. The accumulated pyruvate enters the GABA shunt pathway and is converted to citrate which is acted upon by citrate lyase and converted to acetyl CoA, used for cholesterol synthesis.²⁴ The pyruvate can be converted to glutamate and ammonia which is oxidised by archaea for energy needs. The increased cholesterol substrate leads to increased archaeal growth and digoxin synthesis leading to metabolic channeling to the mevalonate pathway. The archaeal bile acids are steroidal hormones which can bind GPCR and modulate D2 regulating the conversion of T₄ to T₃ which activates uncoupling proteins, can activate NRF $\frac{1}{2}$ inducing NQO1, GST, HOI reducing redox stress, can bind FXR regulating insulin receptor sensitivity and bind PXR inducing the bile acid shunt pathway of cholesterol detoxification.²⁵ This can lead to osteoarthritis and spondylosis. The archaea and viroid induced monocyte activation and Warburg phenotype induced osteoarthritis and spondylosis. A decrease in endosymbiotic archaeal density can lead to osteoporosis. The Warburg phenotype induced increased mitochondrial PT pore hexokinase, archaeal PAH and viroid induced RNA interference can lead on to

oncogene activation important in spondylosis and osteoarthritis. The digoxin and PAH induced increased intracellular calcium can lead to PT pore dysfunction, cell death important in degenerative bone and joint disease.⁴ The archaeal cholesterol catabolism can deplete the cell membranes of cholesterol resulting in organelle dysfunction and degenerative bone and joint disease. The RNA viroids can recombine with HERV sequences and get encapsulated in microvesicles contributing to the retroviral induction. The prion protein conformation is modulated by RNA viroid binding producing prions. Endogenous retrovirus and prionopathies can contribute to osteoarthritis and spondylosis.⁴ Less of endosymbiotic archaeal integration into the genome can produce osteoporosis by the opposite metabolonomic, genomic and immune changes.

The metal actinides provide radiolytic energy, catalysis for oligomer formation and provide a coordinating ion for metalloenzymes all important in abiogenesis.⁷ The metal actinide surfaces would by surface metabolism generate acetate which could get converted to acetyl CoA and then to cholesterol which functions as the primal prebiotic molecule self organizing into self replicating supramolecular systems, the lipid organism.^{9, 26, 27} Cholesterol by radiolysis by actinides would have formed PAH generating PAH aromatic organism.⁹ Cholesterol radiolysis would generate pyruvate which would get converted to amino acids, sugars, nucleotides, porphyrins, fatty acids and TCA acids. Anastase and rutile surfaces can produce polymerization of amino acids, isoprenyl residues, PAH and nucleotides to generate the initial lipid organism, PAH organism, prions and RNA viroids which would have symbiosed to generate the archaeal protocell. The archaea evolved into gram negative and gram positive bacteria with a mevalonate pathway which had a evolutionary advantage and the symbiosis of archaea with gram negative organism generated the eukaryotic cell.²⁸ The data supports the persistence of an actinide and cholesterol based shadow biosphere which throws light on the actinide based origin of life and cholesterol as the premier prebiotic

molecule. Thus the global warming related extent of genomic integration of archaeal DNA contributes to hemispheric dominance and predilection to osteoarthritis, spondylosis and osteoporosis.²⁹⁻³⁶

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