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A Cholesterol and Actinide Dependent Shadow Biosphere of Archaea and Viroids in Neurodegenerative Disorders

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Abstract

Objective: Endogenous digoxin has been related to the pathogenesis of neuronal degeneration.4 The possibility of endogenous digoxin synthesis by actinide based primitive organism like archaea with a mevalonate pathway and cholesterol catabolism was considered.

Methods: 10 cases each of Parkinson's disease, Alzheimer's disease, huntington's disease and motor neuron disease and 10 age and sex matched healthy controls from general population were chosen for the study. Cholesterol substrate was added to the plasma of the patients and the generation of cytochrome F420, free RNA, free DNA, polycyclic aromatic hydrocarbon, hydrogen peroxide, serotonin, pyruvate, ammonia, glutamate, cytochrome C, hexokinase, ATP synthase, HMG CoA redutase, digoxin and bile acids were studied. The changes with the addition of antibiotics and rutile to the patient's plasma were also studied. The statistical analysis was done by ANOVA.

Results: The parameters mentioned above were increased the patient's plasma with addition of cholesterol substrate. The addition of antibiotics to the patient's plasma caused a decrease in all the parameters while addition of rutile increased their levels.

Conclusion: An actinide dependent shadow biosphere of archaea and viroids is described in motor neuron disease, Alzheimer's disease and Parkinson's disease contributing to their pathogenesis.

Key words: Degeneration; Archaea; Viroids; Cholesterol; Actinide

INTRODUCTION

Endomyocardial fibrosis (EMF) along with the root wilt disease of coconut is endemic to Kerala with its radioactive actinide beach sands. Actinides like rutile producing intracellular magnesium deficiency due to rutile-magnesium exchange sites in the cell membrane has been implicated in the etiology of EMF[1]. Endogenous digoxin, a steroidal glycoside which functions as a membrane sodium-potassium ATPase inhibitor has also been related to its etiology due to the intracellular magnesium deficiency it produces.[2] Organisms like phytoplasmas and viroids have also been demonstrated to play a role in the etiology of these diseases.[3,4] Endogenous digoxin has been related to the pathogenesis of neuronal degenerations like parkinson's disease, alzheimer's disease, huntington's disease and motor neuron disease.[2] The possibility of endogenous digoxin synthesis by actinide based primitive organism like archaea with a mevalonate pathway and cholesterol catabolism was considered.[5,6,7] Davies has put forward the concept of a shadow biosphere of organisms with alternate biochemistry present in earth itself.8 An actinide dependent shadow biosphere of archaea and viroids in the above mentioned neuronal degenerations is described.

MATERIALS AND METHODS

Informed consent of the subjects and the approval of the ethics committee were obtained for the study. The following groups were included in the study:- alzheimer's disease, parkinson's disease, huntington's disease and motor neuron disease. 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+ciprofloxacine and doxycycline each in a concentration of 1 mg/ml. Cholesterol substrate was prepared as described by Richmond.[9] Aliquots were withdrawn at zero time immediately after mixing and after incubation at 37^{o}C for 1 hour. The following estimations were carried out:- Cytochrome F420, free RNA, free DNA, polycyclic aromatic hydrocarbon, hydrogen peroxide, dopamine, pyruvate, ammonia, glutamate, cytochrome C, hexokinase, ATP synthase, HMG CoA redutase, digoxin and bile acids.[10,11,12]. Cytochrome F420 was estimated flourimetrically (excitation wavelength 420 nm and emission wavelength 520 nm). Polycyclic aromatic hydrocarbon was estimated by measuring hydrogen peroxide liberated by using glucose reagent. The statistical analysis was done by ANOVA.

RESULTS

The parameters checked as indicated above were:- cytochrome F420, free RNA, free DNA, polycyclic aromatic hydrocarbon, hydrogen peroxide, serotonin, pyruvate, ammonia, glutamate, cytochrome C, hexokinase, ATP synthase, HMG CoA redutase, digoxin and bile acids. 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 rutile increased their levels. The addition of antibiotics to the patient's plasma caused a decrease in all the parameters while addition of rutile 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.

Table 1
Effect of Rutile and Antibiotics on Muramic Acid and Dopamine

	DOPAMINE % (Increase with ce)		DOPAMINE % (Decrease with Doxy)		Muramic acid % (Increase without Doxy)		Muramic acid % (Decrease with Doxy)	
Normal	4.41	0.15	18.63	0.12	4.34	0.15	18.24	0.37
HD	23.79	1.58	65.56	4.03	22.30	2.19	66.19	4.20
AD	23.66	1.67	65.97	3.36	23.09	1.81	65.86	4.27
PD	23.21	1.74	67.76	3.15	22.48	2.13	63.12	4.84
MND	23.89	1.69	65.09	3.89	21.94	2.03	64.29	5.35
Aging	22.71	1.82	66.13	3.83	22.93	2.08	63.49	5.01
F value	403.394		680.284		348.867		364.999	
P value	< 0.001		< 0.001		< 0.001		< 0.001	

Table 2
Effect of Rutile and Antibiotics on Free DNA and RNA

	DNA % change (Increase with rutile)		DNA % change (Decrease with Doxy)		RNA % change (Increase with rutile)		RNA % change (Decrease with Doxy)	
Normal	4.37	0.15	18.39	0.38	4.37	0.13	18.38	0.48
HD	22.48	2.13	63.12	4.84	23.86	1.86	65.93	3.95
AD	23.52	1.65	64.15	4.60	23.29	1.92	65.39	3.95
PD	22.30	2.19	66.19	4.20	23.16	1.60	64.21	3.43
MND	23.11	2.00	61.52	4.97	23.04	1.66	66.13	3.49
Aging	19.73	2.27	65.49	7.28	19.73	2.27	62.70	3.24
F value	337.577		356.621		427.828		654.453	
P value	< 0.001		< 0.001		< 0.001		< 0.001	

Table 3
Effect of Rutile and Antibiotics on HMG CoA Reductase and PAH

	HMG CoA R % change (Increase with Rutile)		HMG CoA R % change (Decrease with Doxy)		PAH % change (Increase with Rutile)		PAH % change (Decrease with Doxy)	
Normal	4.30	0.20	18.35	0.35	4.45	0.14	18.25	0.72
HD	22.86	1.78	61.03	6.13	23.37	1.42	61.01	5.91
AD	23.43	1.68	61.68	8.32	23.26	1.53	60.91	7.59
PD	22.12	2.27	60.98	8.29	23.63	1.75	62.23	5.43
MND	21.79	1.68	64.51	6.96	23.17	2.02	61.03	5.40
Aging	22.94	2.59	59.19	7.18	22.66	1.96	65.88	5.01
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

	Digoxin (ng/ml) (Increase with Rutile)		Digoxin (ng/ml) (Decrease with Doxy+Cipro)		PAH % change (Increase with Rutile)		PAH % change (Decrease with Doxy)	
Normal	0.11	0.00	0.054	0.003	4.29	0.18	18.15	0.58
HD	0.52	0.09	0.177	0.038	23.08	1.56	62.00	5.39
AD	0.55	0.03	0.192	0.040	22.12	2.19	62.86	6.28
PD	0.54	0.03	0.193	0.042	23.77	1.40	65.39	4.88
MND	0.53	0.06	0.229	0.051	23.53	1.78	61.61	6.77
Aging	0.56	0.10	0.238	0.049	24.58	1.08	64.20	5.16
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

	Pyruvate % change (Increase with Rutile)		Pyruvate % change (Decrease with Doxy)		Hexokinase % change (Increase with Rutile)		Hexokinase % change (Decrease with Doxy)	
Normal	4.34	0.21	18.43	0.82	4.21	0.16	18.56	0.76
HD	21.13	1.27	61.54	10.03	22.89	1.88	63.39	4.97
AD	22.63	0.88	56.40	8.59	22.96	2.12	65.11	5.91
PD	21.64	0.67	61.36	8.49	22.95	1.82	64.15	4.62
MND	21.58	0.81	59.11	10.05	23.15	1.78	64.41	4.90
Aging	21.31	2.51	60.42	7.65	23.36	1.78	66.62	4.83
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 Hydrogen Peroxide and Delta Amino Levulinic Acid

	H_2O_2 % (Increase with ce)		H_2O_2 % (Decrease with Doxy)		ALA % (Increase with Rutile)		ALA % (Decrease with Doxy)	
Normal	4.43	0.19	18.13	0.63	4.40	0.10	18.48	0.39
HD	22.27	1.71	60.02	8.51	23.21	1.74	67.76	3.15
AD	22.65	2.48	60.19	6.98	23.67	1.68	66.50	3.58
PD	24.17	1.33	56.09	6.56	23.79	1.58	65.56	4.03
MND	23.58	1.94	57.85	6.63	23.06	1.72	64.82	3.31
Aging	22.27	1.87	61.77	6.79	19.73	2.27	64.78	6.62
F value	380.721		171.228		372.716		556.411	
P value	< 0.001		< 0.001		< 0.001		< 0.001	

Table 7
Effect of Rutile and Antibiotics on ATP Synthase and Cytochrome F 420

	ATP synthase % (Increase with ce)		ATP synthase % (Decrease with Doxy)		CYT F420 % (Increase with Rutile)		CYT F420 % (Decrease with Doxy)	
Normal	4.40	0.11	18.78	0.11	4.48	0.15	18.24	0.66
HD	23.16	1.60	64.21	3.43	22.10	2.83	59.72	6.90
AD	23.58	2.08	66.21	3.69	23.12	2.00	56.90	6.94
PD	23.86	1.86	65.93	3.95	22.32	2.17	57.31	9.22
MND	23.75	1.81	66.49	4.11	22.76	2.20	61.60	8.74
Aging	23.19	1.74	65.68	4.06	22.09	1.38	61.42	7.26
F value	449.503		673.081		306.749		130.054	
P value	< 0.001		< 0.001		< 0.001		< 0.001	

Abbreviations:
HD: Huntington's disease
AD: Alzheimer's disease
MND: Motor neuron disease
PD: Parkinson's disease

DISCUSSION

There was increase in cytochrome F420 indicating archaeal growth in motor neuron disease, parkinson's disease, huntington's disease and alzheimer's disease. The archaea can synthesise and use cholesterol as a carbon and energy source.[13,14] 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.[7] 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 non coding 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.[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, apoptosis, neuronal transmission and euchromatin/ heterochromatin expression. The phenomenon of RNA interference and the RNA viroidal complimentary DNA related jumping genes can lead onto proof reading errors and generation of trinucleotide repeats contributing to the pathogenesis of huntington's disease.

The presence of muramic acid, HMG CoA reductase and cholesterol oxidase activity inhibited by antibiotics indicates the presence of bacteria with mevalonate pathway. The bacterial with mevalonate pathway include streptococcus, staphylococcus, actinomycetes, listeria, coxiella and borrelia.[22] The bacteria and archaea with mevalonate pathway and cholesterol catabolism had a evolutionarily advantage and constitutes the isoprenoidal clade organism with the archaea evolving into mevalonate pathway gram positive and gram negative organism through horizontal gene transfer of viroidal and virus genes.[23] The isoprenoidal clade prokaryotes develop into other groups of prokaryotes via viroidal/virus as well as eukaryotic horizontal gene transfer producing bacterial speciation.[24] The RNA viroids and its complementary DNA developed into cholesterol enveloped RNA and

DNA viruses like herpes, retrovirus, influenza virus, borna virus, cytomegalo virus and Ebstein Barr virus by recombining with eukaryotic and human genes resulting in viral speciation. Bacterial and viral species are ill defined and fuzzy with all of them forming one common genetic pool with frequent horizontal gene transfer and recombination. Thus the multi and unicellular eukaryote with its genes serves the purpose of prokaryotic and viral speciation .The multicellular eukaryote developed so that their endosymbiotic archaeal colonies could survive and forage better .The multicellular eukaryotes are like bacterial biofilms. The archaea and bacteria with a mevalonate pathway uses the extracellular RNA viroids and DNA viroids for quorum sensing and in the generation of symbiotic biofilm like structures which develop into multicellular eukaryotes.[25,26] The endosymbiotic archaea and bacteria with mevalonate pathway still uses the RNA viroids and DNA viroids for the regulation of muticellular eukaryote. Pollution is induced by the primitive nanoarchaea and mevalonate pathway bacteria synthesised PAH and methane leading on to redox stress. Redox stress leads to sodium potassium ATPase inhibition, inward movement of plasma membrane cholesterol, defective SREBP sensing, increased cholesterol synthesis and nanoarchaeal/mevalonate pathway bacterial growth.[27] Redox stress leads on to viroidal and archaeal multiplication. Redox stress can also lead to HERV reverse transcriptase and integrase expression. The noncoding DNA is formed of integrating RNA viroidal complementary DNA and archaea with the integration going on as a continuing event. The archaeal pox like dsDNA virus forms evolutionarily the nucleus .The integrated viroidal, archaeal and mevalonate pathway bacterial sequences can undergo vertical transmission and can exist as genomic parasites. The genomic integrated archaea, mevalonate pathway bacteria and viroids form a genomic reserve of bacteria and viruses which can recombine with human and eukaryotic genes producing bacterial and viral speciation. Bacteria and viruses have been related to the pathogenesis of motor neuron disease, alzheimer's disease and parkinson's disease. Chlamydia, mycoplasma, cyanobacteria, actinomycetes and borrelia have been reported to be involved in the pathogenesis of alzheimer's disease.[28,29,30] Helicobactor pylori, nocardia, streptococcus and corona viruses have been implicated in parkinson's disease.[31,32] Mycoplasma, borrelia, retroviruses and enteroviruses have been related to the pathogenesis of MND.[33,34] The change in the length and grammar of the noncoding region.[35] The integration of nanoarchaea, mevalonate pathway prokaryotes and viroids in to the eukaryotic and human genome produces a chimera which can multiply producing biofilm like multicellular structures having a mixed archaeal, viroidal, prokaryotic and eukaryotic characters which is a regression from the multicellular eukaryotic tissue. This results in a new neuronal, metabolic, immune and tissue phenotype leading to human diseases like neuronal degeneration. The microchimeras formed can lead to polyploidy which has been implicated in degenerations like alzheimer's disease. Microchimeras can lead onto autoimmune disease.

The archaea and viroids can regulate the nervous system including the NMDA transmission.[2] NMDA receptors can be activated by digoxin induced calcium oscillations, PAH increasing NMDA activity as well as viroid induced RNA interference.[2] The cholesterol ring oxidase generated pyruvate can be converted by the GABA shunt pathway to glutamate contributing to NMDA excitotoxicity. The archaea can regulate dopaminergic transmission with archaeal cholesterol aromatase/ring oxidase generated dopamine.[16] The increased dopamine synthesis can generate increased free radicals consequent to its catabolism. Cholesterol oxidase can generate free radical hydrogen peroxide. Free radicals can produce neuronal degeneration. 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.[2] Previous studies by the authors have related right hemispheric chemical dominance to neuronal degeneration. Archaea and RNA viroid can bind the TLR receptor induce NFKB producing immune activation and cytokine TNF alpha secretion. The archaeal DXP and mevalonate pathway metabolites can bind γδ TCR and digoxin induced calcium signaling can activate NFKB producing chronic immune activation.[2,36] The archaea and viroid induced chronic immune activation and generation of superantigens can lead on to autoimmune disease. Immune activation and autoantibodies have been related to neuronal degeneration. Immune activation and free radicals induce neutral sphingomyelinase generating ceramide. Ceramide acts upon the mitochondrial PT pore producing cell death. Archaea, viroids and digoxin can induce the host AKT PI3K, AMPK, HIF alpha and NFKB producing the Warburg metabolic phenotype.[37] 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 resulting in inefficient energetics. Mitochondrial dysfunction has been related to neuronal degeneration. The increased glycolysis results in increased generation of the enzyme glyceraldehyde[3] phosphate dehydrogenase (GAPD). GAPD can undergo polyadenylation via free radical activated PARP enzyme. The polyadenylated GAPD can undergo nuclear translocation producing nuclear cell death. 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.[37] The pyruvate can be converted to glutamate and ammonia which is oxidised by archaea for energy needs. Ammonia can produce NMDA excitotoxicity and cell death. Ammonia can activate sodium potassium ATPase producing increased neuronal requirement of ATP leading onto mitochondrial transmembrane potential changes and cell death. The increased cholesterol substrate leads to increased archaeal growth and digoxin synthesis leading to metabolic channelling to the mevalonate pathway. Digoxin can produce sodium potassium ATPase inhibition and increase in intracellular calcium producing mitochondrial PT pore dysfunction and cell death.2 The archaeal cholesterol catabolism generated PAH can produce NMDA excitoxicity and cell death. The archaeal and mevalonate pathway bacteria cholesterol catabolism can deprive cholesterol from neuronal cell membrane and organelle membranes like mitochondrial, ER and lysosomal membranes producing cellular and organelle dysfunction and death. Cholesterol metabolic defect has been described in huntington's disease. Thus, the shadow biosphere of actinide dependent archaea, viroids and mevalonate pathway bacteria can lead onto neuronal degenerations like alzheimer's disease, huntington's disease, parkinson's disease and motor neuron disease.

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