

## Actinidic Archaea and Viroids Related Hepato-Gastrointestinal Syndrome

Ravikumar Kurup A.<sup>1,\*</sup>; Parameswara Achutha Kurup<sup>1</sup>

<sup>1</sup>Professor of Metabolic Medicine and Neurology, The Metabolic Disorders Research Centre, India

\*Corresponding author.

Address: The Metabolic Disorders Research Centre, TC 4/1525, Gouri Sadan, Kattu Road, North of Cliff House, Kowdiar PO, Trivandrum, Kerala, India

Email: ravikurup13@yahoo.in

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### Abstract

**Background:** Endogenous digoxin has been related to the pathogenesis of cirrhosis liver, ulcerative colitis, irritable bowel syndrome and peptic ulcer disease. The possibility of endogenous digoxin synthesis by archaea with a mevalonate pathway and cholesterol catabolism was considered.

**Methods:** 10 cases each of cirrhosis liver, ulcerative colitis, irritable bowel syndrome and peptic ulcer disease before starting treatment 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 reductase, digoxin and bile acids were studied. The changes with the addition of antibiotics and cerium 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 cerium increased their levels.

**Conclusions:** An actinide dependent shadow biosphere of archaea and viroids is described in cirrhosis liver, ulcerative colitis, irritable bowel syndrome and peptic ulcer disease contributing to their pathogenesis.

**Key words:** Archaea; Viroids; Cirrhosis liver; Ulcerative colitis; Irritable bowel syndrome; Peptic ulcer disease

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### INTRODUCTION

Endomyocardial fibrosis (EMF) along with the root wilt disease of coconut is endemic to Kerala with its radioactive actinide beach sands. Actinides like cerium producing intracellular magnesium deficiency due to cerium-magnesium exchange sites in the cell membrane has been implicated in the etiology of EMF<sup>[1]</sup>. 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<sup>[2]</sup>. Organisms like phytoplasmata and viroids have also been demonstrated to play a role in the etiology of these diseases<sup>[3,4]</sup>. Endogenous digoxin has been related to the pathogenesis of cirrhosis liver, ulcerative colitis, irritable bowel syndrome and peptic ulcer disease<sup>[2]</sup>. The possibility of endogenous digoxin synthesis by actinide based primitive organism like archaea with a mevalonate pathway and cholesterol catabolism was considered<sup>[5,6,7]</sup>. Davies has put forward the concept of a shadow biosphere of organisms with alternate biochemistry present in earth itself<sup>[8]</sup>. An actinide dependent shadow biosphere of archaea and viroids in the above mentioned disease states is described<sup>[6]</sup>.

## 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:- cirrhosis liver, ulcerative colitis, irritable bowel syndrome and peptic ulcer 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+cerium 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<sup>[9]</sup>. 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, muramic acid, polycyclic aromatic hydrocarbon, hydrogen peroxide, serotonin, pyruvate, ammonia, glutamate, cytochrome C, hexokinase, ATP synthase, HMG CoA reductase, digoxin and bile acids<sup>[10,11,12,13]</sup>. 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. The statistical analysis was done by ANOVA.

## RESULTS

The parameters checked as indicated above were:- cytochrome F420, free RNA, free DNA, muramic acid, polycyclic aromatic hydrocarbon, hydrogen peroxide, serotonin, pyruvate, ammonia, glutamate, cytochrome C, hexokinase, ATP synthase, HMG CoA reductase, 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 cerium increased their levels. The addition of antibiotics to the patient's plasma caused a decrease in all the parameters while addition of cerium 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 Cerium and Antibiotics on Muramic Acid and Serotonin

Group	Muramic acid % (Increase with Cerium)		Muramic acid % (Decrease with Doxy+Cipro)		5 HT % (Increase without Doxy)		5 HT % (Decrease with Doxy)	
	Mean	± SD	Mean	± SD	Mean	± SD	Mean	± SD
Normal	4.41	0.15	18.63	0.12	4.34	0.15	18.24	0.37
Cirrhosis	23.11	1.82	66.96	3.79	23.13	1.78	64.88	4.96
PUD	23.43	1.59	65.71	4.01	22.92	1.71	65.58	4.74
UC	23.81	1.45	66.85	3.72	22.83	1.96	63.42	5.10
IBS	23.28	1.95	66.02	3.90	22.79	1.79	62.70	5.05
F value	403.394		680.284		348.867		364.999	
P value	< 0.001		< 0.001		< 0.001		< 0.001	

**Table 2**  
Effect of Cerium and Antibiotics on Free DNA and RNA

Group	DNA % change (Increase with Cerium)		DNA % change (Decrease with Doxy)		RNA % change (Increase with Cerium)		RNA % change (Decrease with Doxy)	
	Mean	± SD	Mean	± SD	Mean	± SD	Mean	± SD
Normal	4.37	0.15	18.39	0.38	4.37	0.13	18.38	0.48
Cirrhosis	22.78	1.94	63.06	6.20	22.91	1.69	66.23	3.44
PUD	23.07	1.50	62.99	5.27	23.32	1.92	66.07	4.11
UC	23.28	1.93	61.81	2.75	22.89	1.85	66.33	3.73
IBS	23.61	1.53	67.77	3.23	22.94	1.88	65.84	4.20
F value	337.577		356.621		427.828		654.453	
P value	< 0.001		< 0.001		< 0.001		< 0.001	

**Table 3**  
**Effect of Cerium and Antibiotics on HMG CoA Reductase and PAH**

	HMG CoA R % change (Increase with Cerium)		HMG CoA R % change (Decrease with Doxy)		PAH % change (Increase with Cerium)		PAH % change (Decrease with Doxy)	
	Normal	4.30	0.20	18.35	0.35	4.45	0.14	18.25
Cirrhosis	23.29	1.67	59.19	7.18	23.39	1.63	65.88	5.01
PUD	23.56	1.83	63.61	6.60	23.06	1.56	64.49	4.64
UC	23.24	1.79	63.55	8.01	23.49	1.48	64.96	5.02
IBS	23.66	1.47	66.11	6.52	23.32	1.46	62.95	7.18
F value	319.332		199.553		391.318		257.996	
P value	< 0.001		< 0.001		< 0.001		< 0.001	

**Table 4**  
**Effect of Cerium and Antibiotics on Digoxin and Bile Acids**

	Digoxin (ng/ml) (Increase with Cerium)		Digoxin (ng/ml) (Decrease with Doxy+Cipro)		Bile acids % change (Increase with Cerium)		Bile acids % change (Decrease with Doxy)	
	Normal	0.11	0.00	0.054	0.003	4.29	0.18	18.15
Cirrhosis	0.50	0.06	0.206	0.034	22.08	1.76	64.20	5.16
PUD	0.50	0.05	0.223	0.025	22.72	1.76	61.84	7.63
UC	0.49	0.06	0.230	0.034	22.30	1.76	62.76	7.49
IBS	0.51	0.06	0.221	0.030	22.62	1.89	63.41	8.47
F value	135.116		71.706		290.441		203.651	
P value	< 0.001		< 0.001		< 0.001		< 0.001	

**Table 5**  
**Effect of Cerium and Antibiotics on Pyruvate and Hexokinase**

	Pyruvate % change (Increase with Cerium)		Pyruvate % change (Decrease with Doxy)		Hexokinase % change (Increase with Cerium)		Hexokinase % change (Decrease with Doxy)	
	Normal	4.34	0.21	18.43	0.82	4.21	0.16	18.56
Cirrhosis	21.52	2.26	60.42	7.65	21.70	1.90	65.26	5.62
PUD	21.29	2.38	57.56	8.70	22.80	2.33	64.43	5.74
UC	21.34	2.24	60.25	8.94	22.29	2.22	65.14	5.66
IBS	20.74	1.47	61.98	6.44	22.36	2.40	63.46	5.69
F value	321.255		115.242		292.065		317.966	
P value	< 0.001		< 0.001		< 0.001		< 0.001	

**Table 6**  
**Effect of Cerium and Antibiotics on Hydrogen Peroxide and Delta Amino Levulinic Acid**

	H <sub>2</sub> O <sub>2</sub> % (Increase with Cerium)		H <sub>2</sub> O <sub>2</sub> % (Decrease with Doxy)		ALA % (Increase with Cerium)		ALA % (Decrease with Doxy)	
	Normal	4.43	0.19	18.13	0.63	4.40	0.10	18.48
Cirrhosis	23.46	1.61	61.77	6.79	23.98	1.72	66.76	4.01
PUD	22.38	1.65	64.59	7.12	23.52	1.74	67.75	3.43
UC	23.65	1.11	59.37	6.93	23.13	1.96	65.86	3.83
IBS	23.22	1.76	59.12	5.14	23.32	1.95	66.69	3.91
F value	380.721		171.228		372.716		556.411	
P value	< 0.001		< 0.001		< 0.001		< 0.001	

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

	ATP synthase % (Increase with Cerium)		ATP synthase % (Decrease with Doxy)		CYT F420 % (Increase with Cerium)		CYT F420 % (Decrease with Doxy)	
	Normal	4.40	0.11	18.78	0.11	4.48	0.15	18.24
Cirrhosis	23.27	1.56	66.43	3.77	22.46	2.39	61.42	7.26
PUD	23.09	1.43	66.43	4.07	22.41	2.02	60.47	8.32
UC	23.14	1.80	66.40	3.64	22.95	1.53	58.86	6.97
IBS	23.16	1.31	67.28	3.54	22.52	1.33	61.43	11.16
F value	449.503		673.081		306.749		130.054	
P value	< 0.001		< 0.001		< 0.001		< 0.001	

## Abbreviations

PUD: Peptic ulcer disease

UC: Ulcerative colitis

IBS: Irritable bowel syndrome

**DISCUSSION**

There was increase in cytochrome F420 indicating archaeal growth in cirrhosis liver, ulcerative colitis, irritable bowel syndrome and peptic ulcer disease. The archaea can synthesise and use cholesterol as a carbon and energy source<sup>[14,15]</sup>. 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 cerium induced increase in enzyme activities<sup>[16]</sup>. 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<sup>[17]</sup>. The archaeal cholesterol oxidase activity was increased resulting in generation of pyruvate and hydrogen peroxide<sup>[15]</sup>. 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<sup>[17]</sup>. 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<sup>[18]</sup>. 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<sup>[19]</sup>. 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<sup>[20]</sup>. 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<sup>[21]</sup>. The integrated viroids and archaea can undergo vertical transmission and can exist as genomic parasites<sup>[20,21]</sup>. This increases the length and alters the grammar of the noncoding region

producing memes or memory of acquired characters<sup>[22]</sup>. The viroidal complementary DNA can function as jumping genes producing a dynamic genome important in HLA gene expression. This modulation of HLA gene expression by viroidal complementary DNA can result in immune activation. The RNA viroids can regulate mrna function by RNA interference<sup>[19]</sup>. The phenomena of RNA interference can modulate T cell and B cell function and euchromatin/heterochromatin expression. RNA viroidal mRNA interference related immune activation plays a role in the pathogenesis of cirrhosis liver, ulcerative colitis, irritable bowel syndrome and peptic ulcer 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<sup>[23]</sup>. 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<sup>[24]</sup>. The isoprenoidal clade prokaryotes develop into other groups of prokaryotes via viroidal/virus as well as eukaryotic horizontal gene transfer producing bacterial speciation<sup>[25]</sup>. 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<sup>[26,27]</sup>. 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<sup>[28]</sup>. 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 cirrhosis liver, ulcerative colitis, irritable bowel syndrome and peptic ulcer disease<sup>[29,30]</sup>. *Helicobacter pylori* has been related to the pathogenesis of peptic ulcer disease<sup>[29]</sup>. Mollicutes, atypical mycobacteria and enterobacteria has been implicated in inflammatory bowel disease<sup>[29,30]</sup>. Gut bacteria and endotoxemia contributes to the pathogenesis of cirrhosis liver<sup>[29]</sup>. Gut bacteria also plays a role in irritable bowel syndrome<sup>[29]</sup>. The change in the length and grammar of the noncoding region produces eukaryotic speciation and individuality<sup>[31]</sup>. Changes in the length of noncoding region especially human endogenous retroviruses can lead onto autoimmune diseases<sup>[32]</sup>. 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 or microchimeras leading to human diseases like cirrhosis liver, ulcerative colitis, irritable bowel syndrome and peptic ulcer disease. The microchimeras formed can lead to autoantigens, immune activation and autoimmune pathology. Autoimmunity has been described in inflammatory bowel disease<sup>[29]</sup>.

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  $\lambda\delta$  TCR and digoxin induced calcium signalling can activate NFKB producing chronic immune activation<sup>[2,33]</sup>. The archaeal cholesterol aromatase generated PAH can produce immune activation. The archaea and viroid induced chronic immune activation and generation of superantigens can lead on to autoimmune disease and immune activation. Immune activation has been related to the pathogenesis of cirrhosis liver, ulcerative colitis, irritable bowel syndrome and peptic ulcer disease<sup>[29,30]</sup>.

The archaea and viroids can regulate the nervous system including the NMDA synaptic transmission<sup>[2]</sup>. NMDA can be activated by digoxin induced calcium oscillations, PAH and viroid induced RNA interference<sup>[2]</sup>. The cholesterol ring oxidase generated pyruvate can be converted by the GABA shunt pathway to glutamate. The

archaeal cholesterol aromatase can generate serotonin<sup>[17]</sup>. Glutamatergic and serotonergic transmission can lead to immune activation which is important in the pathogenesis of cirrhosis liver, ulcerative colitis, irritable bowel syndrome and peptic ulcer disease. Monoamine neurotransmitters and glutamate have been implicated in abnormal gut motility of irritable bowel syndrome. 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<sup>[2]</sup>. Right hemispheric dominance can lead to cirrhosis liver, ulcerative colitis, irritable bowel syndrome and peptic ulcer disease<sup>[2]</sup>.

Archaea, viroids and digoxin can induce the host AKT PI3K, AMPK, HIF alpha and NFKB producing the Warburg metabolic phenotype<sup>[34]</sup>. 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. The lymphocytes depend on glycolysis for their energy needs. The increased glycolysis induced by the Warburg phenotype leads to immune activation. Lactic acid generated by increased glycolysis leads to immune stimulation. Immune activation as noted before is important in the pathogenesis of cirrhosis liver, ulcerative colitis, irritable bowel syndrome and peptic ulcer disease. Cholesterol oxidase activity, increased glycolysis related NADPH oxidase activity, bacterial porphyrin induced redox stress and mitochondrial dysfunction generates free radicals important in the pathogenesis of cirrhosis liver, ulcerative colitis, irritable bowel syndrome and peptic ulcer disease. 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<sup>34</sup>. 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 channelling to the mevalonate pathway. The archaeal cholesterol catabolism can deplete the lymphocytic cell membranes of cholesterol resulting in alteration of lymphocytic cell membrane microdomains related receptors producing immune activation. Hyperdigoxinemia is important in the pathogenesis of cirrhosis liver, ulcerative colitis, irritable bowel syndrome and peptic ulcer disease<sup>[2]</sup>. Digoxin can increase lymphocytic intracellular calcium which leads on to induction of NFKB and immune activation<sup>[2]</sup>. The archaeal bile acids can bind GPCR and modulate D2 regulating the conversion of T4 to T3. T3 activates uncoupling proteins reducing redox stress. Bile acids can also activate NRF  $\frac{1}{2}$  inducing NQO1, GST, HOI reducing redox stress. Bile acids can bind PXR inducing the bile

acid shunt pathway of cholesterol detoxification. Bile acids can bind macrophage GPCR and VDR producing immunosuppression and inhibiting NFKB. This helps to modulate the archaea and viroid induced chronic immune activation. Bile acids are thus protective compounds and put a break on the archaea and viroid induced changes<sup>[35]</sup>. Thus the actinide, viroid and mevalonate pathway bacteria induced metabolic, genetic, immune and neuronal transmission changes can lead onto cirrhosis liver, ulcerative colitis, irritable bowel syndrome and peptic ulcer disease.

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