

Endosymbiotic Actinidic Archaeal Synthesis of Short Chain Fatty Acid Butyrate and Propionate from Cholesterol Regulates Cellular Function

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Abstract

Aims and Objectives: Endomyocardial fibrosis along with the root wilt disease of coconut is endemic to Kerala with its radioactive actinide beach sands. Actinides like rutile as well as organisms like phytoplasmas and viroids have been implicated in the etiology of these diseases. Short chain fatty acids, butyrate and propionate has been related to the pathogenesis of schizophrenia, malignancy, metabolic syndrome x, autoimmune disease and neuronal degeneration. The possibility of short chain fatty acids synthesis by actinide based primitive organism like archaea with a mevalonate pathway and cholesterol catabolism was considered in these disease states.

Methodology: 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. The following estimations were carried out:- Cytochrome F420, butyrate and propionate.

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 rutile increased their levels. The addition of antibiotics and rutile to the patient's plasma produced the same changes but the extent of change was more in patient's sera as compared to

controls.

Conclusion: An actinide dependent shadow biosphere of archaea and viroids in the above mentioned disease states is described. The actinidic archaea by cholesterol side chain oxidation generates butyrate and propionate which can regulate immune, metabolic, neural and genomic function. The generation of short chain fatty acids from cholesterol by actinidic archaea may play a role in disease pathogenesis.

Key words: Archaea; Butyrate; Propionate; Short Chain fatty acid; Cholesterol

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INTRODUCTION

Endomyocardial fibrosis along with the root wilt disease of coconut is endemic to Kerala with its radioactive actinide beach sands. Actinides like rutile as well as organisms like phytoplasmas and viroids have been implicated in the etiology of these diseases^[1,2,3,4]. Short chain fatty acids butyrate and propionate has been related to the pathogenesis of schizophrenia, malignancy, metabolic syndrome x, autoimmune disease and neuronal degeneration^[4]. The actinidic archaea by cholesterol side chain oxidation generates butyrate and propionate which can regulate immune, metabolic, neural and genomic function. The possibility of short chain fatty acids butyrate and propionate synthesis by actinide based primitive organism like archaea with a mevalonate pathway and cholesterol catabolism was considered in this study^[5-8].

MATERIALS AND METHODS

The following groups were included in the study:- endomyocardial fibrosis, alzheimer's disease, multiple sclerosis, non-hodgkin's lymphoma, metabolic syndrome x with cerebrovascular thrombosis and coronary artery disease, schizophrenia, autism, seizure disorder, creutzfeldt jakob disease and acquired immunodeficiency syndrome. 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, butyrate and propionate^[11-13]. Cytochrome F420 was estimated

flourimetrically (excitation wavelength 420 nm and emission wavelength 520 nm). Butyrate and propionate were estimated by HPLC method. 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 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 1-2 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 Cytochrome F420

Group	CYT F420 % (Increase with Rutile)		CYT F420 % (Decrease with Doxy+Cipro)	
	Mean	± SD	Mean	± SD
Normal	4.48	0.15	18.24	0.66
Schizo	23.24	2.01	58.72	7.08
Seizure	23.46	1.87	59.27	8.86
AD	23.12	2.00	56.90	6.94
MS	22.12	1.81	61.33	9.82
NHL	22.79	2.13	55.90	7.29
DM	22.59	1.86	57.05	8.45
AIDS	22.29	1.66	59.02	7.50
CJD	22.06	1.61	57.81	6.04
Autism	21.68	1.90	57.93	9.64
EMF	22.70	1.87	60.46	8.06
		F value 306.749 P value < 0.001	F value 130.054 P value < 0.001	

Table 2
Effect of Rutile and Antibiotics on Butyrate and Propionate Generation from Cholesterol

Group	Butyrate% change (Increase with Rutile)		Butyrate% change (Decrease with Doxy+Cipro)		Propionate % change (Increase with Rutile)		Propionate % change (Decrease with Doxy+Cipro)	
	Mean	± SD	Mean	± SD	Mean	± SD	Mean	± SD
Normal	4.43	0.19	18.13	0.63	4.40	0.10	18.48	0.39
Schizo	22.50	1.66	60.21	7.42	22.52	1.90	66.39	4.20
Seizure	23.81	1.19	61.08	7.38	22.83	1.90	67.23	3.45
AD	22.65	2.48	60.19	6.98	23.67	1.68	66.50	3.58
MS	21.14	1.20	60.53	4.70	22.38	1.79	67.10	3.82
NHL	23.35	1.76	59.17	3.33	23.34	1.75	66.80	3.43
DM	23.27	1.53	58.91	6.09	22.87	1.84	66.31	3.68
AIDS	23.32	1.71	63.15	7.62	23.45	1.79	66.32	3.63
CJD	22.86	1.91	63.66	6.88	23.17	1.88	68.53	2.65
Autism	23.52	1.49	63.24	7.36	23.20	1.57	66.65	4.26
EMF	23.29	1.67	60.52	5.38	22.29	2.05	61.91	7.56
F value 380.721		F value 171.228		F value 372.716		F value 556.411		
P value < 0.001		P value < 0.001		P value < 0.001		P value < 0.001		

DISCUSSION

There was increase in cytochrome F420 indicating archaeal growth. The archaea can synthesise and use cholesterol as a carbon and energy source^[6,14]. The archeal 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^[15,16]. There was an increase in cholesterol side chain oxidation by actinidic archaea. This is indicated by the presence of increasing butyrate and propionate in the system. The cholesterol side chain oxidation generating butyrate and propionate is inhibited by antibiotics and stimulated by rutile. The archaea can undergo magnetite and calcium carbonate mineralization and can exist as calcified nanoforms^[17].

Archaeal butyrate can produce histone deacetylase inhibition resulting in endogenous retroviral (HERV) reverse transcriptase and integrase expression. This can integrate the HERV RNA 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 HERV RNA 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 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 HERV RNA 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 HERV RNA 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.

Butyrate and propionate are histone deacetylase inhibitors. HDAC inhibitors like butyrate can inhibit cell proliferation. Butyrate is used in the treatment of several malignant neoplasms. Butyrate can also modulate protein folding and function. Butyrate can correct the unfolded protein response. Butyrate is thus used in the treatment of disorders with unfolded protein response. This includes disorders like neuronal degeneration and trinucleotide repeat disease.

Butyrate by modulating protein folding is of use in the management of metabolic syndrome x and insulin resistance syndromes. Butyrate and propionate can bind to lymphocyte GPCR receptors. Butyrate and propionate is immunosuppressive and is used in the treatment of autoimmune disease. Archaeal butyrate and propionate deficiency can lead to immune activation and autoimmune disease.

Butyrate can be converted to the inhibitory gamma aminobutyric acid or GABA or the excitatory beta hydroxybutyric acid. Thus butyric acid metabolites can regulate the NMDA/GABA thalamocorticothalamic pathway mediating conscious perception. Butyrate coma has been described. Butyrate can also modulate gene expression related to multiple neurotransmitter systems. Butyrate and propionate are involved in the genesis of neuropsychiatric disorders. Intraventricular propionate has been related to autism and schizophrenia^[22-28].

Thus short chain fatty acids butyrate and propionate can regulate cell death and cell proliferation through modulation of unfold protein response and HDAC inhibition. It can regulate the insulin receptor and protein function by modulating protein folding. Butyrate and propionate via binding to lymphocyte GPCR receptors can regulate immune function. Butyrate can also modulate several neurotransmitter systems including NMDA/GABA. Butyrate by producing HDAC inhibition can regulate gene expression. Thus the archaeal short chain fatty acids butyrate and propionate generated by cholesterol side chain oxidation can regulate the neuro-immune-genetic-endocrine-metabolic system as well as the cell cycle. The archaeal short chain fatty acids may play a role in the pathogenesis of malignancy, degenerations, metabolic syndrome x, autoimmune disease and neuropsychiatric disorders^[22-28].

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