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Endosymbiotic Actinidic Archaeal Synthesis of Pyruvate from Cholesterol and the GABA Shunt Pathway Regulates Cell 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. Cholesterol catabolites have been related to the pathogenesis of schizophrenia, malignancy, metabolic syndrome x, autoimmune disease and neuronal degeneration. The possibility of cholesterol catabolism synthesis by actinide based primitive organism like archaea generating pyruvate and its subsequent channeling to the GABA shunt pathway was evaluated 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+ciprofloxacine and doxycycline each in a concentration of 1 mg/ml. The following estimations were carried out:- Cytochrome F420, pyruvate, H_2O_2, ammonia and glutamate.

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 archaeal cholesterol oxidase converts cholesterol to pyruvate which enters the GABA shunt pathway. This metabolic pathway is crucial in neuroimmunoendocrine integration and plays a role in the pathogenesis of these disease states.

Key words: Actinide; Archaea; GABA Shunt; Pyruvate; Ammonia

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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, endogenous digoxin as well as organisms like phytoplasmas and viroids have been implicated in the etiology of these diseases[1,2,3,4]. Cholesterol catabolism has been related to the pathogenesis of schizophrenia, malignancy, metabolic syndrome x, autoimmune disease and neuronal degeneration[4]. The possibility of cholesterol catabolism synthesis by actinide based primitive organism like archaea generating pyruvate and its subsequent channeling to the GABA shunt pathway was evaluated in these disease states[5-8]. An actinide dependent shadow biosphere of archaea and viroids in the above mentioned disease states is described[7,9].

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+ciprofloxacine 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, hydrogen peroxide, pyruvate, ammonia and glutamate[11-13]. Cytochrome F420 was estimated flourimetrically (excitation wavelength 420 nm and emission wavelength 520 nm). 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 casued 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 1-3 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 Pyruvate and Glutamate

Group	Pyruvate % change (Increase with Rutile)		Pyruvate % change (Decrease with Doxy+Cipro)		Glutamate (Increase with Rutile)		Glutamate (Decrease with Doxy+Cipro)	
	Mean	± SD	Mean	± SD	Mean	± SD	Mean	± SD
Normal	4.34	0.21	18.43	0.82	4.21	0.16	18.56	0.76
Schizo	20.99	1.46	61.23	9.73	23.01	2.61	65.87	5.27
Seizure	20.94	1.54	62.76	8.52	23.33	1.79	62.50	5.56
AD	22.63	0.88	56.40	8.59	22.96	2.12	65.11	5.91
MS	21.59	1.23	60.28	9.22	22.81	1.91	63.47	5.81
NHL	21.19	1.61	58.57	7.47	22.53	2.41	64.29	5.44
DM	20.67	1.38	58.75	8.12	23.23	1.88	65.11	5.14
AIDS	21.21	2.36	58.73	8.10	21.11	2.25	64.20	5.38
CJD	21.07	1.79	63.90	7.13	22.47	2.17	65.97	4.62
Autism	21.91	1.71	58.45	6.66	22.88	1.87	65.45	5.08
EMF	22.29	2.05	62.37	5.05	21.66	1.94	67.03	5.97
	F value 321.255 P value < 0.001		F value 115.242 P value < 0.001		F value 292.065 P value < 0.001		F value 317.966 P value < 0.001	

Table 3
Effect of Rutile and Antibiotics on Hydrogen Peroxide and Ammonia

Group	H_2O_2 % (Increase with Rutile)		H_2O_2 % (Decrease with Doxy+Cipro)		Ammonia % (Increase with Rutile)		Ammonia % (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 P value < 0.001		F value 171.228 P value < 0.001		F value 372.716 P value < 0.001		F value 556.411 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]. The archaeal cholesterol oxidase activity was increased resulting in generation of pyruvate and hydrogen peroxide[14]. The pyruvate gets converted to glutamate by serum glutamate pyruvate transaminase. Glutamate is acted upon by glutamate dehydrogenase generating alpha ketoglutarate and ammonia. Glutamate can also enter the GABA shunt pathway. The glutamate is converted to GABA by the enzyme glutamic acid decarboxylase. GABA is converted to succinic semialdehyde and then succinic acid. Succinic acid enters the TCA sequence. The archaea can undergo magnetite and calcium carbonate mineralization and can exist as calcified nanoforms[17].

Archaeal pyruvate 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[18,19]. 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 HERV RNA complementary DNA 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 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 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. Thus archaeal pyruvate can modulate genomic transmission. The HERV RNA can get encapsulated in microvesicles contributing to the retroviral state. The prion protein conformation is modulated by HERV RNA binding producing prion disease.

Archaeal pyruvate can produce histone deacetylase inhibition which is cytoprotective. Archaeal pyruvate can also function as a free radical scavenger. Archaeal pyruvate can protect against neuronal degeneration. The glutamate generated from pyruvate can produce glutamate excitotoxicity and neuronal degeneration. The ammonia generated by the action of glutamate dehydrogenase has got multiple actions. The ammonia increases sodium-potassium ATPase activity which increases mitochondrial function, cell exhaustion and cell death. The ammonia has got a biphasic action in that it can stimulate the NMDA receptor producing glutamate excitotoxicity. Ammonia can therefore act as a gasotransmitter. The ammonia generated can play a role in neuronal degeneration.

The archaea and viroids can regulate the nervous system including the NMDA/GABA thalamocorticothalamic pathway mediating conscious perception[4, 22]. The cholesterol ring oxidase generated pyruvate can be converted by the GABA shunt pathway to glutamate and GABA. The glutamate dehydrogenase generated ammonia can stimulate both the GABA and NMDA receptor acting as a gasotransmitter. The cholesterol ring oxidase generated H_2O_2 can increase NMDA transmission and activate GAD generating GABA. Thus the H_2O_2, ammonia, glutamate and GABA generated by pyruvate metabolism can modulate the thalamocorticothalamic pathway. The dipolar archaeal magnetite in the setting of cholesterol oxidase generated H_2O_2 and glutamate dehydrogenase generated ammonia induced sodium potassium ATPase inhibition can produce a pumped phonon system mediated frohlich model superconducting state[22] inducing quantal perception with nanoarchaeal sensed gravity producing the orchestrated reduction of the quantal possibilities to the macrosopic world[4,22]. The archaeal pyruvate can get converted to acetyl CoA and acetyl choline. Acetyl choline is the principal neurotransmitter mediating memory and cognition. Acetyl choline is also the principal parasympathetic neurotransmitter regulating the visceral system. 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 mediated NMDA transmission producing schizophrenia and autism.

The archaeal pyruvate and alpha ketoglutarate generated by the action of GDH on glutamate can suppress NFKB producing immunosuppression and decrease in cytokine secretion. The succinate generated by the GABA shunt pathway can activate the immune system and increase cytokine secretion. Thus the metabolites immunosuppressive pyruvate/alpha ketoglutarate and immunostimulatory succinate has a regulatory role on the immune system. The disruption of metabolic balance between pyruvate/alpha ketoglutarate and succinate can lead to autoimmune disease. The ammonia generated by the action of GDH is immunosuppressive. The H_2O_2

generated by action of cholesterol oxidase can activate NFKB. Thus the gasotransmitters NH_3 and H_2O_2 can also regulate the immune system[4,23]. The archaeal pyruvate can get converted to acetyl CoA and acetyl choline. Acetyl choline stimulates the vagal system which is immunosuppressive.

Archaea pyruvate gets converted to glutamate. Glutamate gets acted upon by GDH to generate alpha ketoglutarate. Glutamate can enter the GABA shunt pathway generating succinate. Alpha ketoglutarate inhibits the transcription factor HIF alpha. Succinate stimulates the transcription factor HIF alpha. Activation of HIF alpha stimulates glycolysis, inhibits pyruvate dehydrogenase, stimulates heme oxygenase, stimulates VEGF and activates NOS. Thus the activation of HIF alpha by succinate generates the Warburg phenotype with increased glycolysis. This can lead to increased cell proliferation and malignant transformation. The mitochondrial PT pore hexokinase is increased leading onto cell proliferation. The increase in glycolysis can activate glyceraldehyde 3 phosphate dehydrogenase which gets translocated to the nucleus after polyadenylation. This can produce nuclear cell death and neuronal degeneration. The increase in the glycolytic enzyme fructose 1,6 diphosphatase increases the pentose phosphate pathway. This generates NADPH which activates NOX. NOX activation is related to NMDA activation and glutamate excitotoxicity. This leads onto neuronal degeneration. The lymphocytes depends on glycolysis for its energy needs. The increase in glycolysis owing to the induction of Warburg phenotype can lead to immune activation. NOX activation consequent to the generation of the Warburg phenotype also activates the insulin receptor. Pyruvate and succinate can increase insulin secretion from the beta cells of the pancreas. Thus there is a hyperinsulinemic state leading on to metabolic syndrome x. Thus the induction of the Warburg phenotype by succinate generated via the GABA shunt pathway can lead to malignancy, autoimmune disease, metabolic syndrome x, neuropsychiatric disease and neuronal degeneration[24].

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. Thus there is also an increased cholesterol and lipid synthesis consequent to induction of the Warburg phenotype. The increase in cholesterol synthesis leads to more of archaeal growth.

Thus the archaeal cholesterol oxidase generated pyruvate can fuel the GABA shunt pathway generating the Warburg phenotype and contribute to the pathogenesis of schizophrenia, malignancy, metabolic syndrome x, autoimmune disease and neuronal degeneration.

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