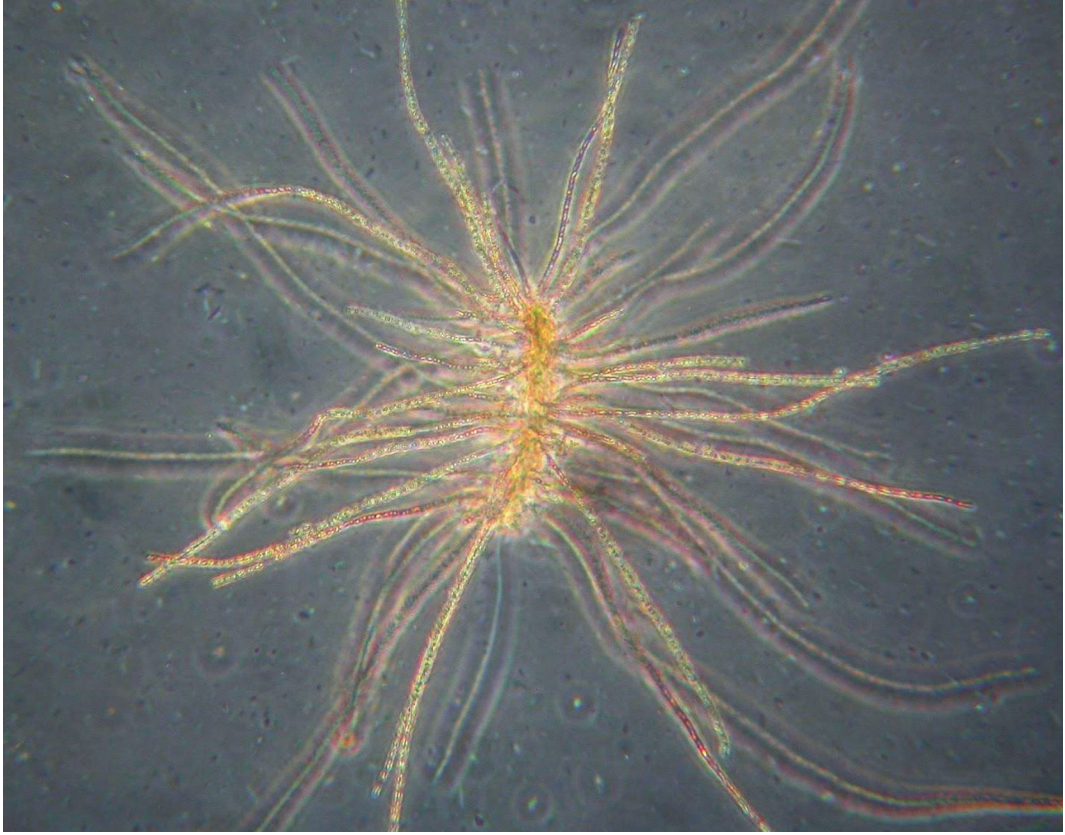

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ISBN: 978-1-941926-60-4

Published in 2016 by Open Science Publishers
228 Park Ave., S#45956, New York, NY 10003, U.S.A.
http://www.openscienceonline.com

Contents

Introduction

Endosymbiotic neuronal archaea can produce cerebellar cognitive affective disorder. It can lead to an autonomic neuropathy with sympathetic overactivity and parasympathetic suppression. This leads to metabolic syndrome x, cancer, neurodegeneration, schizophrenia, autism and autoimmune disease. Archaea can synthesize porphyrins from cholesterol. The cholesterol ring is catabolized to pyruvate which then enters the GABA shunt pathway generating succinyl CoA and glycine the substrates for porphyrin synthesis. The increased amounts of porphyrins in the system leads to absorption of low level EMF leading to prefrontal cortex atrophy and cerebellar dominance. Cerebellar dominance leads to activation of sympathetic system and parasympathetic suppression. The archaea produces the Warburg phenotype by inducing HIF alpha. This results in inhibition of PDH resulting in defective formation of acetyl CoA and acetyl choline producing a parasympathetic neuropathy. The archaeal porphyrins can produce reactive oxygen species by photooxidation resulting in stress and sympathetic overactivity creating an excess of epinephrine, norepinephrine and dopamine. Stress and sympathetic overactivity as well as elevated cortisol can lead to beta amyloid accumulation. This can lead to neurodegeneration. Sympathetic overactivity can produce vasospasm leading onto coronary artery disease and stroke. Sympathetic overactivity and vagal block can produce defective insulin secretion and diabetes mellitus. This contributes to the genesis of metabolic syndrome x. Sympathetic overactivity and vagal block can produce immune activation and autoimmune disease. Immunity is regulated by a vagal reflex. Sympathetic overactivity and parasympathetic blockade can lead to cell proliferation and malignant transformation. Stress induced sympathetic overactivity and cholinergic underactivity can contribute to autism and schizophrenia. Thus an archaeal induced autonomic neuropathy with sympathetic overactivity and parasympathetic blockade can contribute to systemic disease.

This results from the archaeal induced Warburg phenotype and PDH blockade resulting in defective acetyl CoA formation as well as increased prophyrinogenesis occurring via the GABA shunt pathway.

Chapter 1

Porphyrions - Relation to CVS-pulmonary-Git Dysautonomia, Coronary/Cerebral Microangiopathy, Polyendocrine Failure and Chronic Fatigue/Panic Syndrome Complex

Introduction

Actinidic archaea is described as an endosymbiont in humans and can induce porphyrinuria in humans. The study aims to relate actinidic archaea to the pathogenesis of migraine, bronchial asthma, essential hypertension with cardiac autonomic neuropathy, irritable bowel syndrome, inflammatory bowel disease, sexual dysautonomia, peptic ulcer disease, polyendocrine failure, Hashimoto's encephalopathy, microangiopathic cerebral/coronary disease, normal pressure hydrocephalus, panic syndrome and chronic fatigue syndrome. An actinide dependent shadow biosphere of archaea and viroids in the above mentioned disease states is described. Actinidic archaea have a mevalonate pathway and are cholesterol catabolizing. They can use cholesterol as a carbon and energy source. Archaeal cholesterol catabolism can generate porphyrins via the cholesterol ring oxidase generated pyruvate and GABA shunt pathway. Archaea can produce a secondary porphyria by inducing the enzyme heme oxygenase resulting in heme depletion and activation of the enzyme ALA synthase. The study also aims to relate porphyrins to the pathogenesis of migraine, bronchial asthma, essential hypertension with cardiac autonomic neuropathy, irritable bowel syndrome, inflammatory bowel disease, sexual dysautonomia, peptic ulcer disease, polyendocrine failure, Hashimoto's encephalopathy, microangiopathic cerebral / coronary disease, normal pressure hydrocephalus, panic syndrome and chronic fatigue syndrome. This syndrome complex with porphyrinuria can exist as isolated entities or in differing combinations. It constitutes an acquired porphyrin metabolic defect resulting from growth of endosymbiontic actinidic archaea as well as due to environmental pollution. Environmental pollution with pesticides and toxins induces cytochrome P450 enzyme resulting in heme deficiency, ALA synthase induction and porphyrin synthesis. This can be considered as a disorder

of civilizational progress. The role of archaeal porphyrins in regulation of cell functions and neuro-immuno-endocrine integration is discussed. A porphyrin metabolic dysfunction related CVS-pulmonary-GIT dysautonomia, coronary/cerebral microangiopathy, polyendocrine failure and chronic fatigue/panic syndrome complex is described.[1-5] They can function as self replicating supramolecular organisms which can be called as porphyrions.

Materials and Methods

The following groups were included in the study: - (1) migraine, (2) bronchial asthma, (3) essential hypertension and cardiac autonomic neuropathy (4) irritable bowel syndrome, (5) inflammatory bowel disease (6) peptic ulcer disease, (7) sexual dysautonomia (8) polyendocrine failure, (9) Hashimoto's encephalopathy, (10) microangiopathic cerebral / coronary disease, (11) normal pressure hydrocephalus, (12) panic syndrome and (13) chronic fatigue 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. There were also 10 normal people with right hemispheric dominance, left hemispheric dominance and bi-hemispheric dominance drawn 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. Aliquots were withdrawn at zero time immediately after mixing and after incubation at 37 ℃ for 1 hour. The following estimations were carried out: - Cytochrome F420, free RNA, free DNA, polycyclic aromatic hydrocarbon, hydrogen peroxide, pyruvate, ammonia,

glutamate, delta aminolevulinic acid, succinate, glycine and digoxin. 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 study also involved estimating the following parameters in the patient population - digoxin, bile acid, hexokinase, porphyrins, pyruvate, glutamate, ammonia, acetyl CoA, acetyl choline, HMG CoA reductase, cytochrome C, blood ATP, ATP synthase, ERV RNA (endogenous retroviral RNA), H_2O_2 (hydrogen peroxide), NOX (NADPH oxidase), TNF alpha and heme oxygenase.[6-9] 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 section 1: tables 1-6 as percentage change in the parameters after 1 hour incubation as compared to the values at zero time. There was upregulated archaeal porphyrin synthesis in the patient population which was archaeal in origin as indicated by actinide catalysis of the reactions. The cholesterol oxidase pathway generated

pyruvate which entered the GABA shunt pathway. This resulted in synthesis of succinate and glycine which are substrates for ALA synthase.

The study showed the patient's blood and right hemispheric dominance had increased heme oxygenase activity and porphyrins. The hexokinase activity was high. The pyruvate, glutamate and ammonia levels were elevated indicating blockade of PDH activity, and operation of the GABA shunt pathway. The acetyl CoA levels were low and acetyl choline was decreased. The cyto C levels were increased in the serum indicating mitochondrial dysfunction suggested by low blood ATP levels. This was indicative of the Warburg's phenotype. There were increased NOX and TNF alpha levels indicating immune activation. The HMG CoA reductase activity was high indicating cholesterol synthesis. The bile acid levels were low indicating depletion of cytochrome P450. The normal population with right hemispheric dominance had values resembling the patient population with increased porphyrin synthesis. The normal population with left hemispheric dominance had low values with decreased porphyrin synthesis.

Section 1: Experimental Study

Table 1. *Effect of rutile and antibiotics on cytochrome F420 and PAH.*

Group	CYT F420 % (Increase with Rutile)		CYT F420 % (Decrease with Doxy+Cipro)		PAH % change (Increase with Rutile)		PAH % change (Decrease with Doxy+Cipro)	
	Mean	± SD	Mean	± SD	Mean	± SD	Mean	± SD
Normal	4.48	0.15	18.24	0.66	4.45	0.14	18.25	0.72
Migraine	23.24	2.01	58.72	7.08	23.01	1.69	59.49	4.30
BA	23.46	1.87	59.27	8.86	22.67	2.29	57.69	5.29
HBP	23.12	2.00	56.90	6.94	23.26	1.53	60.91	7.59
IBD/IBS	22.12	1.81	61.33	9.82	22.83	1.78	59.84	7.62
PUD	22.79	2.13	55.90	7.29	22.84	1.42	66.07	3.78
CFS	22.59	1.86	57.05	8.45	23.40	1.55	65.77	5.27
HE/NPH	22.29	1.66	59.02	7.50	23.23	1.97	65.89	5.05
CAD/CVA	22.06	1.61	57.81	6.04	23.46	1.91	61.56	4.61
Endo failure	21.68	1.90	57.93	9.64	22.61	1.42	64.48	6.90
Panic attacks	22.70	1.87	60.46	8.06	23.73	1.38	65.20	6.20
F value	306.749		130.054		391.318		257.996	
P value	< 0.001		< 0.001		< 0.001		< 0.001	

Table 2. *Effect of rutile and antibiotics on free RNA and DNA.*

Group	DNA % change (Increase with Rutile)		DNA % change (Decrease with Doxy+Cipro)		RNA % change (Increase with Rutile)		RNA % change (Decrease with Doxy+Cipro)	
	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
Migraine	23.28	1.70	61.41	3.36	23.59	1.83	65.69	3.94
BA	23.40	1.51	63.68	4.66	23.08	1.87	65.09	3.48
HBP	23.52	1.65	64.15	4.60	23.29	1.92	65.39	3.95
IBD/IBS	22.62	1.38	63.82	5.53	23.29	1.98	67.46	3.96
PUD	22.42	1.99	61.14	3.47	23.78	1.20	66.90	4.10
CFS	23.01	1.67	65.35	3.56	23.33	1.86	66.46	3.65
HE/NPH	22.56	2.46	62.70	4.53	23.32	1.74	65.67	4.16
CAD/CVA	23.30	1.42	65.07	4.95	23.11	1.52	66.68	3.97
Endo failure	22.12	2.44	63.69	5.14	23.33	1.35	66.83	3.27
Panic attacks	22.29	2.05	58.70	7.34	22.29	2.05	67.03	5.97
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 digoxin and delta aminolevulinic acid.*

Group	Digoxin (ng/ml) (Increase with Rutile)		Digoxin (ng/ml) (Decrease with Doxy+Cipro)		ALA % (Increase with Rutile)		ALA % (Decrease with Doxy+Cipro)	
	Mean	± SD	Mean	± SD	Mean	± SD	Mean	± SD
Normal	0.11	0.00	0.054	0.003	4.40	0.10	18.48	0.39
Migraine	0.55	0.06	0.219	0.043	22.52	1.90	66.39	4.20
BA	0.51	0.05	0.199	0.027	22.83	1.90	67.23	3.45
HBP	0.55	0.03	0.192	0.040	23.67	1.68	66.50	3.58
IBD/IBS	0.52	0.03	0.214	0.032	22.38	1.79	67.10	3.82
PUD	0.54	0.04	0.210	0.042	23.34	1.75	66.80	3.43
CFS	0.47	0.04	0.202	0.025	22.87	1.84	66.31	3.68
HE/NPH	0.56	0.05	0.220	0.052	23.45	1.79	66.32	3.63
CAD/CVA	0.53	0.06	0.212	0.045	23.17	1.88	68.53	2.65
Endo failure	0.53	0.08	0.205	0.041	23.20	1.57	66.65	4.26
Panic attacks	0.51	0.05	0.213	0.033	22.29	2.05	61.91	7.56
F value	135.116		71.706		372.716		556.411	
P value	< 0.001		< 0.001		< 0.001		< 0.001	

Table 4. *Effect of rutile and antibiotics on succinate and glycine.*

Group	Succinate % (Increase with Rutile)		Succinate % (Decrease with Doxy+Cipro)		Glycine % change (Increase with Rutile)		Glycine % change (Decrease with Doxy+Cipro)	
	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
Migraine	22.76	2.20	67.63	3.52	22.79	2.20	64.26	6.02
BA	22.28	1.52	64.05	2.79	22.82	1.56	64.61	4.95
HBP	23.81	1.90	66.95	3.67	23.12	1.71	65.12	5.58
IBD/IBS	24.10	1.61	65.78	4.43	22.73	2.46	65.87	4.35
PUD	23.43	1.57	66.30	3.57	22.98	1.50	65.13	4.87
CFS	23.70	1.75	68.06	3.52	23.81	1.49	64.89	6.01
HE/NPH	23.66	1.67	65.97	3.36	23.09	1.81	65.86	4.27
CAD/CVA	22.92	2.14	67.54	3.65	21.93	2.29	63.70	5.63
Endo failure	21.88	1.19	66.28	3.60	23.02	1.65	67.61	2.77
Panic attacks	22.29	1.33	65.38	3.62	22.13	2.14	66.26	3.93
F value	403.394		680.284		348.867		364.999	
P value	< 0.001		< 0.001		< 0.001		< 0.001	

Table 5. *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
Migraine	20.99	1.46	61.23	9.73	23.01	2.61	65.87	5.27
BA	20.94	1.54	62.76	8.52	23.33	1.79	62.50	5.56
HBP	22.63	0.88	56.40	8.59	22.96	2.12	65.11	5.91
IBD/IBS	21.59	1.23	60.28	9.22	22.81	1.91	63.47	5.81
PUD	21.19	1.61	58.57	7.47	22.53	2.41	64.29	5.44
CFS	20.67	1.38	58.75	8.12	23.23	1.88	65.11	5.14
HE/NPH	21.21	2.36	58.73	8.10	21.11	2.25	64.20	5.38
CAD/CVA	21.07	1.79	63.90	7.13	22.47	2.17	65.97	4.62
Endo failure	21.91	1.71	58.45	6.66	22.88	1.87	65.45	5.08
Panic attacks	22.29	2.05	62.37	5.05	21.66	1.94	67.03	5.97
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 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
Migraine	22.50	1.66	60.21	7.42	22.52	1.90	66.39	4.20
BA	23.81	1.19	61.08	7.38	22.83	1.90	67.23	3.45
HBP	22.65	2.48	60.19	6.98	23.67	1.68	66.50	3.58
IBD/IBS	21.14	1.20	60.53	4.70	22.38	1.79	67.10	3.82
PUD	23.35	1.76	59.17	3.33	23.34	1.75	66.80	3.43
CFS	23.27	1.53	58.91	6.09	22.87	1.84	66.31	3.68
HE/NPH	23.32	1.71	63.15	7.62	23.45	1.79	66.32	3.63
CAD/CVA	22.86	1.91	63.66	6.88	23.17	1.88	68.53	2.65
Endo failure	23.52	1.49	63.24	7.36	23.20	1.57	66.65	4.26
Panic attacks	23.29	1.67	60.52	5.38	22.29	2.05	61.91	7.56
F value	380.721		171.228		372.716		556.411	
P value	< 0.001		< 0.001		< 0.001		< 0.001	

Abbreviations

BA: Bronchial asthma

HBP: Hypertension

IBD: Inflammatory bowel disease

IBS: Irritable bowel syndrome

PUD: Peptic ulcer disease

CFS: Chronic fatigue syndrome

HE: Hashimoto’s encephalopathy

NPH: Normal pressure hydrocephalus

CAD: Microangiopathic coronary artery disease

CVA: Microangiopathic cerebrovascular disease

Section 2: Patient Study

Table 1

Group	RBC Digoxin (ng/ml RBC Susp)		Cytochrome F 420		HERV RNA (ug/ml)		H_2O_2 (umol/ml RBC)	
	Mean	± SD	Mean	± SD	Mean	± SD	Mean	± SD
NO/BHCD	0.58	0.07	1.00	0.00	17.75	0.72	177.43	6.71
RHCD	1.41	0.23	4.00	0.00	55.17	5.85	278.29	7.74
LHCD	0.18	0.05	0.00	0.00	8.70	0.90	111.63	5.40
Migraine	1.38	0.26	4.00	0.00	51.17	3.65	274.88	8.73
Bronchial asthma	1.23	0.26	4.00	0.00	50.04	3.91	278.90	11.20
Hypertension/CAN	1.34	0.31	4.00	0.00	51.16	7.78	295.37	3.78
IBS	1.10	0.08	4.00	0.00	51.56	3.69	277.47	10.90
IBD	1.21	0.21	4.00	0.00	47.90	6.99	280.89	11.25
PUD	1.50	0.33	4.00	0.00	48.20	5.53	278.59	11.51
NPH with HE	1.26	0.23	4.00	0.00	51.08	5.24	283.39	10.67
Panic syndrome	1.27	0.24	4.00	0.00	51.57	2.66	278.19	12.80
CFS	1.35	0.26	4.00	0.00	51.98	5.05	280.89	10.58
CAD	1.22	0.16	4.00	0.00	50.00	5.91	280.89	13.79
CVA	1.33	0.27	4.00	0.00	51.06	4.83	287.33	9.47
Polyendocrine failure	1.31	0.24	4.00	0.00	50.15	6.96	278.58	12.72
Sexual dysautonomia	1.48	0.27	4.00	0.00	49.85	6.40	286.16	10.90
F value	60.288		0.001		194.418		713.569	
P value	< 0.001		< 0.001		< 0.001		< 0.001	

Table 2

Group	NOX (OD diff/hr/mgpro)		TNF ALP (pg/ml)		ALA (umol24)		PBG (umol24)	
	Mean	**± SD**	**Mean**	**± SD**	**Mean**	**± SD**	**Mean**	**± SD**
NO/BHCD	0.012	0.001	17.94	0.59	15.44	0.50	20.82	1.19
RHCD	0.036	0.008	78.63	5.08	63.50	6.95	42.20	8.50
LHCD	0.007	0.001	9.29	0.81	3.86	0.26	12.11	1.34
Migraine	0.036	0.009	78.23	7.13	66.16	6.51	42.50	3.23
Bronchial asthma	0.038	0.007	79.28	4.55	68.28	6.02	46.54	4.55
Hypertension/CAN	0.035	0.011	82.13	3.97	67.30	5.98	47.25	4.19
IBS	0.036	0.007	79.65	5.57	67.32	5.40	49.83	3.45
IBD	0.034	0.009	80.18	5.67	64.00	7.33	46.85	3.49
PUD	0.038	0.008	81.03	6.22	65.01	5.42	48.55	3.81
NPH with HE	0.041	0.006	77.98	5.68	63.21	6.55	47.17	4.86
Panic syndrome	0.038	0.007	79.18	5.88	67.67	5.69	46.84	4.43
CFS	0.041	0.005	78.36	6.68	64.72	6.81	48.15	3.36
CAD	0.038	0.009	78.15	3.72	66.66	7.77	47.00	3.81
CVA	0.037	0.007	77.59	5.24	69.02	4.86	46.33	4.01
Polyendocrine failure	0.039	0.010	79.17	5.88	67.78	4.41	48.03	3.64
Sexual dysautonomia	0.039	0.006	80.41	5.70	66.99	3.71	47.94	5.33
F value	44.896		427.654		295.467		183.296	
P value	< 0.001		< 0.001		< 0.001		< 0.001	

Table 3

Group	Uroporphyrin (nmol24)		Coproporphyrin (nmol/24)		Protoporphyrin (Ab unit)		Heme (uM)	
	Mean	**± SD**	**Mean**	**± SD**	**Mean**	**± SD**	**Mean**	**± SD**
NO/BHCD	50.18	3.54	137.94	4.75	10.35	0.38	30.27	0.81
RHCD	250.28	23.43	389.01	54.11	42.46	6.36	12.47	2.82
LHCD	9.51	1.19	64.33	13.09	2.64	0.42	50.55	1.07
Migraine	267.81	64.05	401.49	50.73	44.30	2.66	12.82	2.40
Bronchial asthma	290.44	57.65	436.71	52.95	49.59	1.70	13.03	0.70
Hypertension/CAN	286.84	24.18	432.22	50.11	49.36	4.18	11.81	0.80
IBS	259.61	33.18	433.17	45.61	49.68	3.30	12.09	1.12
IBD	277.36	15.48	440.35	25.34	50.81	3.21	11.87	1.84
PUD	294.51	58.62	447.39	39.84	52.94	3.67	12.95	1.53
NPH with HE	310.25	40.44	495.98	39.11	54.80	4.04	11.76	1.37
Panic syndrome	304.19	14.16	479.35	58.86	53.73	5.34	13.68	1.67
CFS	285.46	29.46	422.27	33.86	49.80	4.01	12.83	2.07
CAD	314.01	17.82	426.14	24.28	49.51	2.27	11.39	1.10
CVA	320.85	24.73	402.16	33.80	46.74	4.28	11.26	0.95
Polyendocrine failure	306.61	22.47	429.72	24.97	49.32	5.13	11.60	1.23
Sexual dysautonomia	317.92	29.63	429.24	18.29	50.02	4.58	11.76	1.32
F value	160.533		279.759		424.198		1472.05	
P value	< 0.001		< 0.001		< 0.001		< 0.001	

Table 4

Group	Bilirubin (mg/dl)		Biliverdin (Ab unit)		ATP Synthase (umol/gHb)		SE ATP (umol/dl)	
	Mean	**± SD**	**Mean**	**± SD**	**Mean**	**± SD**	**Mean**	**± SD**
NO/BHCD	0.55	0.02	0.030	0.001	0.36	0.13	0.42	0.11
RHCD	1.70	0.20	0.067	0.011	2.73	0.94	2.24	0.44
LHCD	0.21	0.00	0.017	0.001	0.09	0.01	0.02	0.01
Migraine	1.74	0.08	0.073	0.013	2.66	0.58	1.26	0.19
Bronchial asthma	1.84	0.07	0.070	0.015	3.09	0.65	1.66	0.56
Hypertension/CAN	1.83	0.09	0.071	0.014	3.34	0.84	1.27	0.26
IBS	1.77	0.13	0.073	0.016	3.34	0.75	2.06	0.19
IBD	1.81	0.10	0.079	0.007	3.05	0.52	1.63	0.26
PUD	1.82	0.08	0.061	0.006	2.85	0.34	1.59	0.22
NPH with HE	1.84	0.08	0.077	0.011	3.01	0.55	1.73	0.26
Panic syndrome	1.76	0.11	0.073	0.012	2.70	0.62	1.48	0.32
CFS	1.77	0.19	0.067	0.014	3.19	0.89	1.97	0.11
CAD	1.75	0.12	0.080	0.007	2.99	0.65	1.57	0.37
CVA	1.82	0.10	0.079	0.009	2.98	0.78	1.49	0.27
Polyendocrine failure	1.79	0.08	0.072	0.013	3.29	0.63	1.59	0.38
Sexual dysautonomia	1.82	0.09	0.066	0.009	3.21	0.95	1.69	0.43
F value	370.517		59.963		54.754		67.588	
P value	< 0.001		< 0.001		< 0.001		< 0.001	

Table 5

Group	Cyto C (ng/ml)		Lactate (mg/dl)		Pyruvate (umol/l)		RBC Hexokinase (ug glu phos/ hr/mgpro)	
	Mean	± SD	Mean	± SD	Mean	± SD	Mean	± SD
NO/BHCD	2.79	0.28	7.38	0.31	40.51	1.42	1.66	0.45
RHCD	12.39	1.23	25.99	8.10	100.51	12.32	5.46	2.83
LHCD	1.21	0.38	2.75	0.41	23.79	2.51	0.68	0.23
Migraine	11.58	0.90	22.07	1.06	96.54	9.96	7.69	3.40
Bronchial asthma	12.06	1.09	21.78	0.58	90.46	8.30	6.29	1.73
Hypertension/CAN	12.65	1.06	24.28	1.69	95.44	12.04	9.30	3.98
IBS	11.94	0.86	22.04	0.64	97.26	8.26	8.46	3.63
IBD	11.81	0.67	23.32	1.10	102.48	13.20	8.56	4.75
PUD	11.73	0.56	23.06	1.49	100.51	9.79	8.02	3.01
NPH with HE	11.91	0.49	22.83	1.24	95.81	12.18	7.41	4.22
Panic syndrome	13.00	0.42	22.20	0.85	96.58	8.75	7.82	3.51
CFS	12.95	0.56	25.56	7.93	96.30	10.33	7.05	1.86
CAD	11.51	0.47	22.83	0.82	97.29	12.45	8.88	3.09
CVA	12.74	0.80	23.03	1.26	103.25	9.49	7.87	2.72
Polyendocrine failure	12.29	0.89	24.87	4.14	95.55	7.20	9.84	2.43
Sexual dysautonomia	12.19	1.22	23.02	1.61	96.50	5.93	8.81	4.26
F value	445.772		162.945		154.701		18.187	
P value	< 0.001		< 0.001		< 0.001		< 0.001	

Table 6

Group	ACOA (mg/dl)		ACH (ug/ml)		Glutamate (mg/dl)	
	Mean	**± SD**	**Mean**	**± SD**	**Mean**	**± SD**
NO/BHCD	8.75	0.38	75.11	2.96	0.65	0.03
RHCD	2.51	0.36	38.57	7.03	3.19	0.32
LHCD	16.49	0.89	91.98	2.89	0.16	0.02
Migraine	2.51	0.57	48.52	6.28	3.41	0.41
Bronchial asthma	2.15	0.22	33.27	5.99	3.67	0.38
Hypertension/CAN	1.95	0.06	35.02	5.85	3.14	0.32
IBS	2.19	0.15	42.84	8.26	3.53	0.39
IBD	2.03	0.09	39.99	12.61	3.58	0.36
PUD	2.54	0.38	49.30	7.26	3.37	0.38
NPH with HE	2.30	0.26	50.58	3.82	3.48	0.46
Panic syndrome	2.34	0.43	42.51	11.58	3.28	0.39
CFS	2.17	0.40	41.31	10.69	3.53	0.44
CAD	2.37	0.44	49.19	6.86	3.61	0.28
CVA	2.25	0.44	37.45	7.93	3.31	0.43
Polyendocrine failure	2.11	0.19	38.40	7.74	3.45	0.49
Sexual dysautonomia	2.10	0.27	34.97	4.24	3.94	0.22
F value	1871.04		116.901		200.702	
P value	< 0.001		< 0.001		< 0.001	

Table 7

Group	Se. Ammonia (ug/dl)		HMG Co A (HMG CoA/MEV)		Bile Acid (mg/ml)	
	Mean	**± SD**	**Mean**	**± SD**	**Mean**	**± SD**
NO/BHCD	50.60	1.42	1.70	0.07	79.99	3.36
RHCD	93.43	4.85	1.16	0.10	25.68	7.04
LHCD	23.92	3.38	2.21	0.39	140.40	10.32
Migraine	94.72	3.28	1.11	0.08	22.45	5.57
Bronchial asthma	95.61	7.88	1.14	0.07	22.98	5.19
Hypertension/CAN	94.60	8.52	1.08	0.13	28.93	4.93
IBS	95.37	4.66	1.10	0.07	26.26	7.34
IBD	93.42	3.69	1.13	0.08	24.12	6.43
PUD	101.18	17.06	1.14	0.07	19.62	1.97
NPH with HE	91.62	3.24	1.12	0.10	23.45	5.01
Panic syndrome	93.20	4.46	1.10	0.09	23.43	6.03
CFS	93.38	7.76	1.09	0.12	22.77	4.94
CAD	93.93	4.86	1.07	0.12	24.55	6.26
CVA	103.18	27.27	1.05	0.09	22.39	3.35
Polyendocrine failure	92.47	3.97	1.08	0.11	23.28	5.81
Sexual dysautonomia	93.13	5.79	1.09	0.12	21.26	4.81
F value	61.645		159.963		635.306	
P value	< 0.001		< 0.001		< 0.001	

Abbreviations

NO/BHCD: Normal/Bi-hemispheric chemical dominance

RHCD: Right hemispheric chemical dominance

LHCD: Left hemispheric chemical dominance

CAN: Coronary autonomic neuropathy

IBS: Irritable bowel syndrome

IBD: Inflammatory bowel disease

PUD: Peptic ulcer disease

NPH with HE: Normal pressure hydrocephalus with Hashimoto's encephalopathy

CFS: Chronic fatigue syndrome

CAD: Microangiopathic coronary artery disease

CVA: Microangiopathic cerebrovascular disease

Discussion

There was increase in cytochrome F420 indicating archaeal growth. The archaea can synthesize and use cholesterol as a carbon and energy source.[2, 10] 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.[11] The archaeal beta hydroxyl steroid dehydrogenase activity indicating digoxin synthesis.[12] The archaeal cholesterol oxidase activity was increased resulting in generation of pyruvate and hydrogen peroxide.[10] The pyruvate gets converted to glutamate and

ammonia by the GABA shunt pathway. The pyruvate is converted to glutamate by serum glutamate pyruvate transaminase. The glutamate gets acted upon by glutamate dehydrogenase to generate alpha ketoglutarate and ammonia. Alanine is most commonly produced by the reductive amination of pyruvate via alanine transaminase. This reversible reaction involves the interconversion of alanine and pyruvate, coupled to the interconversion of alpha-ketoglutarate (2-oxoglutarate) and glutamate. Alanine can contribute to glycine. Glutamate is acted upon by Glutamic acid decarboxylase to generate GABA. GABA is converted to succinic semialdehyde by GABA transaminase. Succinic semialdehyde is converted to succinic acid by succinic semialdehyde dehydrogenase. Glycine combines with succinyl CoA to generate delta aminolevulinic acid catalysed by the enzyme ALA synthase. There was upregulated archaeal porphyrin synthesis in the patient population which was archaeal in origin as indicated by actinide catalysis of the reactions. The cholesterol oxidase pathway generated pyruvate which entered the GABA shunt pathway. This resulted in synthesis of succinate and glycine which are substrates for ALA synthase. The archaea can undergo magnetite and calcium carbonate mineralization and can exist as calcified nanoforms.[13]

The porphyrins can contribute to the pathogenesis of migraine, bronchial asthma, essential hypertension, irritable bowel syndrome, inflammatory bowel disease, sexual dysautonomia, peptic ulcer disease, polyendocrine failure, Hashimoto's encephalopathy, microangiopathic cerebral / coronary disease, normal pressure hydrocephalus, panic syndrome and chronic fatigue syndrome. The porphyrins can undergo photo-oxidation and auto-oxidation generating free radicals. The archaeal porphyrins can produce free radical injury. The porphyrin photo-oxidation generated free radicals which can modulate enzyme function. Redox stress modulated enzymes include pyruvate dehydrogenase, nitric oxide synthase, cystathione beta synthase and heme oxygenase. Free radicals can

modulate mitochondrial PT pore function. Free radicals can modulate cell membrane function and inhibit sodium potassium ATPase activity. Free radicals produce NFKB activation, open the mitochondrial PT pore resulting in cell death, produce oncogene activation, activate NMDA receptor and GAD enzyme regulating neurotransmission and generates the Warburg phenotypes activating glycolysis and inhibiting TCA cycle/oxphos. Redox stress induced by porphyrin auto-oxidation is crucial to the pathogenesis of these functional disorders. The porphyrins can complex and intercalate with the cell membrane producing sodium potassium ATPase inhibition adding on to digoxin mediated inhibition. Porphyrin induced sodium potassium ATPase inhibition can increase the intracellular calcium load as well as produce intracellular magnesium depletion which are crucial to the pathogenesis of these functional disorders. Increased calcium load and magnesium depletion in the cell produce vasospasm, bronchospasm, bowel motility dysfunction, immune activation and mitochondrial dysfunction. Porphyrins can complex with proteins and nucleic acid producing biophoton emission. Porphyrins complexing with proteins can modulate protein structure and function. Porphyrins complexing with DNA and RNA can modulate transcription and translation. Porphyrin modulating protein, DNA and RNA function can contribute to the pathogenesis of these functional disorders. The porphyrin especially protoporphyrins can bind to peripheral benzodiazepine receptors in the mitochondria and modulate its function, mitochondrial cholesterol transport and steroidogenesis. Defective mitochondrial steroidogenesis can contribute to endocrine failure. Peripheral benzodiazepine receptor modulation by protoporphyrins can regulate cell death, cell proliferation, immunity and neural functions. The protoporphyrin modulation of the peripheral benzodiazepine receptors is important in the pathogenesis of these functional disorders.[3-5] 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 and porphyrins 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. Archaeal pyruvate producing histone deacetylase inhibition and porphyrins intercalating with DNA can produce 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. The archaea and viroids can also induce cellular porphyrin synthesis. Bacterial and viral infections can precipitate porphyria. Thus porphyrins can regulate genomic function. The viroids and HERV RNA can modulate mRNA function by RNA interference. The viroids and HERV RNA can contribute to the pathogenesis of migraine, bronchial asthma, essential hypertension, irritable bowel syndrome, inflammatory bowel disease, sexual dysautonomia, peptic ulcer disease, polyendocrine failure, Hashimoto's encephalopathy, microangiopathic cerebral/coronary disease, normal pressure hydrocephalus, panic syndrome and chronic fatigue syndrome. Thus the porphyrins are key regulatory molecules modulating all aspects of cell function.[14, 15]

The possibility of Warburg phenotype induced by actinide based primitive organism like archaea with a mevalonate pathway and cholesterol catabolism contributing the pathogenesis of migraine, bronchial asthma, essential hypertension with cardiac autonomic neuropathy, irritable bowel syndrome, inflammatory bowel disease, sexual dysautonomia, peptic ulcer disease, polyendocrine failure, Hashimoto's encephalopathy, microangiopathic cerebral/coronary disease, normal pressure hydrocephalus, panic syndrome and chronic fatigue syndrome is important. The Warburg phenotype results in

inhibition of pyruvate dehydrogenase and the TCA cycle. The pyruvate enters the GABA shunt pathway where it is converted to succinyl CoA. The glycolytic pathway is upregulated and the glycolytic metabolite phosphoglycerate is converted to serine and glycine. Glycine and succinyl CoA are the substrates for ALA synthesis. The archaea induces the enzyme heme oxygenase. Heme oxygenase converts heme to bilirubin and biliverdin. This depletes heme from the system and results in upregulation of ALA synthase activity resulting in porphyria. Heme inhibits HIF alpha. The heme depletion results in upregulation of HIF alpha activity and further strengthening of the Warburg phenotype. The porphyrin self oxidation results in redox stress which activates HIF alpha and generates the Warburg phenotype. The Warburg phenotype results in channelling acetyl CoA for cholesterol synthesis as the TCA cycle and mitochondrial oxidative phosphorylation are blocked. The archaea uses cholesterol as an energy substrate. Porphyrin and ALA inhibits sodium potassium ATPase. This increases cholesterol synthesis by acting upon intracellular SREBP. The cholesterol is metabolized to pyruvate and then the GABA shunt pathway for ultimate use in porphyrin synthesis. The porphyrins can self organize and self replicate into macromolecular arrays. The porphyrin arrays behave like an autonomous organism and can have intramolecular electron transport generating ATP. The porphyrin macroarrays can store information and can have quantal perception. The porphyrin macroarrays serves the purpose of archaeal energetics and sensory perception. The Warburg phenotype is associated with migraine, bronchial asthma, essential hypertension, irritable bowel syndrome, inflammatory bowel disease, sexual dysautonomia, peptic ulcer disease, polyendocrine failure, Hashimoto's encephalopathy, microangiopathic cerebral / coronary disease, normal pressure hydrocephalus, panic syndrome and chronic fatigue syndrome. The increased generation of fructose 1,6 diphosphate and its channelling to the pentose phosphate pathway

generates NADPH activating NOX. NOX activation generates H_2O_2 induced redox stress contributing to induction of NFKB and immune activation. The lymphocytes depend exclusively on glycolysis for its energy needs. The upregulation of glycolysis produces immune activation. Immune activation and cytokine injury can contribute to the pathogenesis of these functional disorders. NOX induced redox stress mediated by H_2O_2 can contribute to the pathogenesis of these functional disorders. Warburg phenotype associated mitochondrial dysfunction is crucial to the pathogenesis of migraine, bronchial asthma, essential hypertension, irritable bowel syndrome, inflammatory bowel disease, sexual dysautonomia, peptic ulcer disease, polyendocrine failure, Hashimoto's encephalopathy, microangiopathic cerebral/coronary disease, normal pressure hydrocephalus, panic syndrome and chronic fatigue syndrome.

The role of archaeal porphyrins in regulation of cell functions and neuro-immuno-endocrine integration is discussed. Protoporphyrin binds to the peripheral benzodiazepine receptor regulating steroid and digoxin synthesis. Increased porphyrin metabolites can contribute to hyperdigoxinemia. Digoxin can modulate the neuro-immuno-endocrine system. Digoxin can produce membrane sodium potassium ATPase inhibition increasing intracellular calcium and reducing intracellular magnesium. Porphyrins can combine with membranes modulating membrane function and producing sodium potassium ATPase inhibition. Digoxin induced intracellular calcium load can activate NFKB producing cytokine injury as well as produce mitochondrial dysfunction. Digoxin induced increased intracellular calcium can produce vasospasm and bronchospasm. Digoxin induced mitochondrial dysfunction can produce redox stress. Hyperdigoxinemia is related to the pathogenesis of migraine, bronchial asthma, essential hypertension, irritable bowel syndrome, inflammatory bowel disease, sexual dysautonomia, peptic ulcer disease, polyendocrine failure, Hashimoto's encephalopathy, microangiopathic cerebral/coronary disease,

normal pressure hydrocephalus, panic syndrome and chronic fatigue syndrome. These groups of functional disorders can be classified as intracellular calcium overload and magnesium depleted states.

Porphyrins can combine with proteins oxidizing their tyrosine, tryptophan, cysteine and histidine residues producing crosslinking and altering protein conformation and function. This can produce a protein processing dysfunction and defectively processed proteins accumulate in the cell. Porphyrin induced protein processing dysfunction and defective protein function can contribute to migraine, bronchial asthma, essential hypertension, irritable bowel syndrome, inflammatory bowel disease, sexual dysautonomia, peptic ulcer disease, polyendocrine failure, Hashimoto's encephalopathy, microangiopathic cerebral/coronary disease, normal pressure hydrocephalus, panic syndrome and chronic fatigue syndrome. Porphyrins can complex with DNA and RNA modulating their function. Porphyrin interpolating with DNA can alter transcription and generate HERV expression. HERV RNA can produce mRNA interference affecting its function. HERV expression can also contribute to the pathogenesis of these functional disorders.

Heme deficiency can also result in disease states. Heme deficiency results in deficiency of heme enzymes. There is deficiency of cytochrome C oxidase and mitochondrial dysfunction. Mitochondrial dysfunction induced energy depletion and redox stress is crucial to the pathogenesis of these functional disorders. Mitochondrial dysfunction induced muscle weakness is crucial in chronic fatigue syndrome. The glutathione peroxidase is dysfunctional and the glutathione system of free radical scavenging does not function. Redox stress is crucial to the pathogenesis of these functional disorders. The cytochrome P450 enzymes involved in steroid and bile acid synthesis have reduced activity leading to steroid - cortisol, activated vitamin D and sex hormones as well as

bile acid deficiency states. Heme deficiency also results in defective thyroid peroxidase function and thyroid hormone deficiency. Deficiency of cortisol, thyroid and sex hormones produce the syndrome of endocrine failure. Bile acid deficiency and activated vitamin D deficiency are important in the evolution of these disorders. Activated vitamin D and bile acid like lithocholic acid bind to VDR modulating the immune system. Activated vitamin D deficiency as well as bile acid deficiency can lead to immune activation and cytokine injury important in the pathogenesis of these functional disorders. The heme deficiency results in dysfunction of nitric oxide synthase, heme oxygenase and cystathione beta synthase resulting in lack of gasotransmitters regulating the vascular system and NMDA receptor - NO, CO and H_2S. Heme has got cytoprotective, neuroprotective, anti-inflammatory and antiproliferative effects. Deficiency of NO, CO and H_2S which are vasodilatory gasotransmitters can contribute to hypertension, cardiac autonomic neuropathy and sexual dysautonomia. Sexual dysautonomia combined with gonadal failure can contribute to infertility and asexuality. Heme is also involved in the stress response. Deficient heme induced stress response can lead to panic attacks. Heme deficiency leads to migraine, bronchial asthma, essential hypertension, irritable bowel syndrome, inflammatory bowel disease, sexual dysautonomia, peptic ulcer disease, polyendocrine failure, Hashimoto's encephalopathy, microangiopathic cerebral/coronary disease, normal pressure hydrocephalus, panic syndrome and chronic fatigue syndrome.[3-5]

Porphyrins can lead on to an immune activated state. The porphyrin photo-oxidation can generate free radicals which can activate NFKB. This can produce immune activation and cytokine mediated injury. The protoporphyrins binding to mitochondrial benzodiazepine receptors can modulate immune function. Porphyrins can combine with proteins oxidizing their tyrosine, tryptophan, cysteine and histidine residues producing crosslinking and altering

protein conformation and function. Porphyrins can complex with DNA and RNA modulating their structure. Porphyrin complexed with proteins and nucleic acids are antigenic and can lead onto autoimmune disease.[3, 4] Immune activation and autoimmunity is crucial to migraine, bronchial asthma, essential hypertension, irritable bowel syndrome, inflammatory bowel disease, sexual dysautonomia, peptic ulcer disease, polyendocrine failure, Hashimoto's encephalopathy, microangiopathic cerebral/coronary disease, normal pressure hydrocephalus, panic syndrome and chronic fatigue syndrome. Porphyrins can lead on to an insulin resistance state. The porphyrin photo-oxidation mediated free radical injury can lead to insulin resistance and atherogenesis. Thus archaeal porphyrins can contribute to metabolic syndrome x. Glucose has got a negative effect upon ALA synthase activity. Therefore hyperglycemia may be reactive protective mechanism to increased archaeal porphyrin synthesis. The protoporphyrins binding to mitochondrial benzodiazepine receptors can modulate mitochondrial steroidogenesis and metabolism. Altered porphyrin metabolism has been described in the metabolic syndrome x. Porphyrias can lead onto vascular thrombosis.[3, 4] Insulin resistance states have been related to migraine, bronchial asthma, essential hypertension, irritable bowel syndrome, inflammatory bowel disease, sexual dysautonomia, peptic ulcer disease, polyendocrine failure, Hashimoto's encephalopathy, microangiopathic cerebral / coronary disease, normal pressure hydrocephalus, panic syndrome and chronic fatigue syndrome. The porphyrin photo-oxidation can generate free radicals inducing HIF alpha and producing oncogene activation. Heme deficiency can lead to activation of HIF alpha and oncogenesis. This can lead to oncogenesis. All these functional disorders can lead to malignant transformations as in the case of IBD. The protoporphyrins binding to mitochondrial benzodiazepine receptors can regulate cell proliferation.[3, 4] The porphyrins can intercalate with DNA producing HERV expression. The HERV particles generated can

contribute to the retroviral state. All these functional disorders are associated with the retroviral state. The porphyrins in the blood can combine with bacteria and viruses and the photo-oxidation generated free radicals can kill them. The archaeal porphyrins can modulate bacterial and viral infections. The archaeal porphyrins are regulatory molecules keeping other prokaryotes and viruses on check.[3, 4] Bacterial and viral infections have been related to migraine, bronchial asthma, essential hypertension, irritable bowel syndrome, inflammatory bowel disease, sexual dysautonomia, peptic ulcer disease, polyendocrine failure, Hashimoto's encephalopathy, microangiopathic cerebral/coronary disease, normal pressure hydrocephalus, panic syndrome and chronic fatigue syndrome. *H. pylori* infection can lead to peptic ulcer disease.[3, 4]

The archaea and viroids can regulate the nervous system including the NMDA/GABA thalamo-cortico-thalamic pathway mediating conscious perception. Porphyrin photooxidation can generate free radicals which can modulate NMDA transmission. Free radicals can increase NMDA transmission. Free radicals can induce GAD and increase GABA synthesis. ALA blocks GABA transmission and upregulates NMDA. Protoporphyrins bind to GABA receptor and promote GABA transmission. Thus porphyrins can modulate the thalamo-cortico-thalamic pathway of conscious perception. The dipolar porphyrins, PAH and archaeal magnetite in the setting of digoxin induced sodium potassium ATPase inhibition can produce a pumped phonon system mediated Frohlich model superconducting state inducing quantal perception with nanoarchaeal sensed gravity producing the orchestrated reduction of the quantal possibilities to the macroscopic world. ALA can produce sodium potassium ATPase inhibition resulting in a pumped phonon system mediated quantal state involving dipolar porphyrins. Porphyrin molecules have a wave particle existence and can bridge the dividing line between quantal state and particulate state. Thus the porphyrins can mediate conscious and quantal

perception. Porphyrins binding to proteins, nucleic acids and cell membranes can produce biophoton emission. Porphyrins by auto-oxidation can generate biophotons and are involved in quantal perception. Biophotons can mediate quantal perception. Cellular porphyrins photo-oxidation are involved in sensing of earth magnetic fields and low level biomagnetic fields. Thus prophyrins can mediate extrasensory perception. The porphyrins can modulate hemispheric dominance. There is increased porphyrin synthesis and RHCD and decreased porphyrin synthesis in LHCD. Porphyria can lead to psychiatric disorders and seizures. Right hemispheric chemical dominance is related to migraine, bronchial asthma, essential hypertension, irritable bowel syndrome, inflammatory bowel disease, sexual dysautonomia, peptic ulcer disease, polyendocrine failure, Hashimoto's encephalopathy, microangiopathic cerebral/coronary disease, normal pressure hydrocephalus, panic syndrome and chronic fatigue syndrome. All these functional disorders have a neuropsychiatric substratum.

Protoporphyrins block acetyl choline transmission producing a vagal neuropathy with sympathetic overactivity. This can lead to panic syndrome, coronary autonomic neuropathy and hypertension. Vagal neuropathy results in immune activation, vasospasm and vascular disease. A vagal neuropathy underlines metabolic syndrome x and microangiopathic disease. Vagal neuropathy induced immune activation can produce cytokine injury crucial in the pathogenesis of migraine, bronchial asthma, essential hypertension, irritable bowel syndrome, inflammatory bowel disease, sexual dysautonomia, peptic ulcer disease, polyendocrine failure, Hashimoto's encephalopathy, microangiopathic cerebral/coronary disease, normal pressure hydrocephalus, panic syndrome and chronic fatigue syndrome. Porphyrin induced increased NMDA transmission and free radical injury can contribute to cell death. Free radicals can produce mitochondrial PT pore dysfunction. This can lead to cyto

C leak and activation of the caspase cascade leading to apoptosis and cell death. Porphyrin induced cell death can contribute to the pathogenesis of these disorders. The protoporphyrins binding to mitochondrial benzodiazepine receptors can regulate brain function and cell death.[3, 4, 16]

The dipolar porphyrins, PAH and archaeal magnetite in the setting of digoxin induced sodium potassium ATPase inhibition can produce a pumped phonon system mediated Frohlich model superconducting state inducing quantal perception with nanoarchaeal sensed gravity producing the orchestrated reduction of the quantal possibilities to the macroscopic world. ALA can produce sodium potassium ATPase inhibition resulting in a pumped phonon system mediated quantal state involving dipolar porphyrins. Porphyrins by autooxidation can generate biophotons and are involved in quantal perception. Biophotons can mediate quantal perception. Cellular porphyrins photo-oxidation are involved in sensing of earth magnetic fields and low level biomagnetic fields. Porphyrins can thus contribute to quantal perception. Low level electromagnetic fields and light can induce porphyrin synthesis. Low level EMF can produce ferrochelatase inhibition as well as heme oxygenase induction contributing to heme depletion, ALA synthase induction and increased porphyrin synthesis. Light also induces ALA synthase and porphyrin synthesis. The increased porphyrin synthesized can contribute to increased quantal perception and can modulate conscious perception. The porphyrin induced biophotons and quantal fields can modulate the source from which low level EMF and photic fields were generated. Thus the porphyrin generated by extraneous low level EMF and photic fields can interact with the source of low level EMF and photic fields modulating it. Thus porphyrins can serve as a bridge between the human brain and the source of low level EMF and photic fields. This serves as a mode of communication between the human brain and EMF storage devices like internet. The porphyrins can also serve as the source

of communication with the environment. Environmental EMF and chemicals produce heme oxygenase induction and heme depletion increasing porphyrin synthesis, quantal perception and two-way communication. Thus induction of porphyrin synthesis can serve as a mechanism of communication between human brain and the environment by extrasensory perception. Low level of EMF exposure can lead to migraine, bronchial asthma, essential hypertension with cardiac autonomic neuropathy, irritable bowel syndrome, inflammatory bowel disease, sexual dysautonomia, peptic ulcer disease, polyendocrine failure, Hashimoto's encephalopathy, microangiopathic cerebral/coronary disease, normal pressure hydrocephalus, panic syndrome and chronic fatigue syndrome. All these functional disorders are increasing in epidemic proportions and environmental pollution with low level of EMF is related to it. These functional disorders are related to civilizational progress.

Porphyrins also have evolutionary significance since porphyria is related to Scythian races and contributes to the behavioural and intellectual characteristics of this group of population. Porphyrins can intercalate into DNA and produce HERV expression. HERV RNA can get converted to DNA by reverse transcriptase which can get integrated into DNA by integrase. This tends to increase the length of the non-coding region of the DNA. The increase in non-coding region of the DNA is involved in primate and human evolution. Thus, increased rates of porphyrin synthesis would correlate with increase in non-coding DNA length. The alteration in the length of the non coding region of the DNA contributes to the dynamic nature of the genome. Thus genetic and acquired porphyrias can lead to alteration in the non-coding region of the genome. The alteration of the length of the non-coding region of the DNA contributes to the racial and individual differences in populations. An increased length of non-coding region as well as increased porphyrin synthesis leads to increased cognitive and creative neuronal function. Porphyrins are involved in

quantal perception and regulation of the thalamo-cortico-thalamic pathway of conscious perception. Thus genetic and acquired porphyrias contribute to higher cognitive and creative capacity of certain races. Porphyrias are common among Eurasian Scythian races who have assumed leadership roles in communities and groups. Porphyrins have contributed to human and primate evolution. Scythian races have a higher incidence of migraine, bronchial asthma, essential hypertension with cardiac autonomic neuropathy, irritable bowel syndrome, inflammatory bowel disease, sexual dysautonomia, peptic ulcer disease, polyendocrine failure, Hashimoto's encephalopathy, microangiopathic cerebral/coronary disease, normal pressure hydrocephalus, panic syndrome and chronic fatigue syndrome. Most of our patient population belonged to this group.[3, 4]

An actinide dependent shadow biosphere of archaea and viroids in the above mentioned disease states - migraine, bronchial asthma, essential hypertension with cardiac autonomic neuropathy, irritable bowel syndrome, inflammatory bowel disease, sexual dysautonomia, peptic ulcer disease, polyendocrine failure, Hashimoto's encephalopathy, microangiopathic cerebral/coronary disease, normal pressure hydrocephalus, panic syndrome and chronic fatigue syndrome is described. Porphyrin synthesis is crucial in the pathogenesis of these disorders. Porphyrins may serve as regulatory molecules modulating immune, neural, endocrine, metabolic and genetic systems. The porphyrins photo-oxidation generated free radicals can produce immune activation, produce cell death, activate cell proliferation, produce insulin resistance and modulate conscious/quantal perception. The archaeal porphyrins functions as key regulatory molecules with mitochondrial benzodiazepine receptors playing an important role. The porphyrins photo-oxidation generated free radicals can produce immune activation, produce cell death, activate cell proliferation, produce insulin resistance and modulate conscious/quantal perception.

Porphyrins can regulate hemispheric dominance. Porphyrins inhibit cholinergic transmission producing a vagal neuropathy and sympathetic overactivity. Heme deficiency can induce the Warburg phenotype contributing to the pathogenesis. Heme deficiency also results in mitochondrial dysfunction as well as dysfunction of the glutathione system of free radicals scavenging. Heme deficiency can affect thyroid peroxidase and cytochrome P450 enzymes involved in steroidal synthesis producing a polyendocrine failure. Heme deficiency can affect the heme enzymes producing the vasodilatory gasotransmitter NO, CO and H_2S synthesis producing hypertension and erectile dysfunction. The gonadal failure with erectile dysfunction can lead on to asexual personality. Porphyrin generated redox stress can induce NFKB producing immune activation. Vagal neuropathy and gasotransmitter deficiency especially of NO can lead to microangiopathic of the coronary and cerebral circulation. Vagal neuropathy can also contribute to immune activation. Immune activation can contribute to IBD. Gasotransmitter deficiency and immune activation can induce IBS. Immune activation leading to an immune mediated aseptic meningitis and vagal neuropathy related microangiopathic disease are causal factors for normal pressure hydrocephalus. Immune activation consequent to vagal neuropathy and redox stress as well as heme deficiency related mitochondrial dysfunction can lead to chronic fatigue syndrome. Vagal neuropathy with sympathetic overactivity can induce to panic attacks. Redox stress and immune activation can lead to migraine and bronchial asthma. Protoporhyrin mediated increased digoxin synthesis can contribute to increased intracellular calcium producing hypertension, bronchial asthma and migraine. The archaeal porphyrins functions as key regulatory molecules with mitochondrial benzodiazepine receptors playing an important role. A porphyrin metabolic defect underlies the pathogenesis of migraine, bronchial asthma, essential hypertension with cardiac autonomic neuropathy, irritable bowel

syndrome, inflammatory bowel disease, sexual dysautonomia, peptic ulcer disease, polyendocrine failure, Hashimoto's encephalopathy, microangiopathic cerebral/coronary disease, normal pressure hydrocephalus, panic syndrome and chronic fatigue syndrome. This can be called as a civilizational porphyrin metabolic disorder. A porphyrin metabolic dysfunction related CVS-pulmonary-GIT dysautonomia, coronary/cerebral microangiopathy, polyendocrine failure and chronic fatigue/panic syndrome complex is described.

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Chapter 2

Neanderthal Hybrids
and Dysautonomic Syndrome

Introduction

There is a high incidence of autism and Neanderthal anthropometric phenotypes in the Nair community of Kerala. The Nair community is matrilineal and is one of the few functional matriarchies in the world and speaks the Dravidian language with similarities to Celtic, Scythian, Berber and Basque societies. The autistic brain is comparable to the large sized Neanderthal brain. Autistic metabolonomic patterns include low efficiency pyruvate dehydrogenase activity, mitochondrial dysfunction, dominant GABA shunt, Warburg glycolytic phenotype, hyperammonemia, hyperhomocysteinemia, porphyria, low cholesterol and bile acid levels. Similar pattern of autistic metabolonomics is seen in the normal nair population of Kerala. Neanderthal metabolonomic patterns include a low efficiency PDH activity. Autistic and matrilineal societies like nair can be considered as fossilized remnants of the Neanderthal population. Endosymbiotic actinidic archaea using cholesterol as an energy substrate has been described in systemic disease from our laboratory. The autistic and Nair population have increased actinide dependent cytochrome F420 activity suggestive of endosymbiotic archaeal growth. Archaeal induced PDH and mitochondrial suppression results in the autistic metabolonomic cascade. The increased archaeal growth in extremophilic conditions of the Ice age would have contributed to the evolution of Neanderthal population. The autistic metabolonomic patterns are also seen in syndrome x, schizophrenia, cancer, multiple sclerosis and Alzheimer's disease. There is a rising epidemic of these civilizational diseases and could indicate neanderthalisation of the human species due to global warming, extreme climate change and archaeal growth. Global warming itself could be construed as due to increased archaeal growth and methanogenesis. It would indicate the

emergence of cultural, linguistic, psychological, neurological, metabolic, immune and anthropometric phenotype - homo archaeax neanderthalis.

Materials and Methods

Four groups, 25 numbers in each group were chosen for the study - the autistic population diagnosed according to DSM criteria, the normal Nair population, the normal non-Nair population and civilizational disease group including metabolic syndrome x, Alzheimer's disease, cancer, schizophrenia and multiple sclerosis. The matrilineal characteristics and Neanderthal anthropometric characteristics of normal Nair and non-Nair population as well as autistic population were studied. The blood samples were drawn in the fasting state before treatment was initiated. The estimations done in the blood samples collected include cytochrome F420 activity, cholesterol oxidase activity - cholesterol ring oxidase activity, cholesterol side chain oxidase activity and cholesterol aromatase activity, digoxin, lactate, pyruvate, ammonia, ATP, glutamate, acetyl CoA, acetyl choline, ALA, homocysteine, cholesterol and bile acid levels as well as cyto C and hexokinase levels activity. Archaeal cholesterol catabolism was studied as follows - 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+ciprofloxacine and doxycycline each in a concentration of 1 mg/ml. Cholesterol substrate was prepared as described by Richmond. Aliquots were withdrawn at zero time immediately after mixing and after incubation at 37 ℃ for 1 hour. The following estimations were carried out: - Cytochrome F420, polycyclic aromatic hydrocarbon, hydrogen peroxide, pyruvate, ammonia, glutamate, digoxin, butyrate, propionate and bile acids. 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. 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 and Discussion

The results of the study were as follows. The Nair, autistic and civilizational disease group had (1) increased cytochrome F420 activity, cholesterol oxidase activity, ring oxidase activity, aromatase activity and digoxin synthesis (2) had decreased PDH activity as indicated by increased pyruvate and lactate levels with low acetyl CoA levels (3) had increased glycolysis as indicated by increased hexokinase activity and mitochondrial dysfunction as noted by increased cyto C activity in the serum and low ATP levels (4) had low cholesterol and bile acid levels and increased homocysteine levels (5) had increased GABA shunt pathway as indicated by increased pyruvate, glutamate and ammonia levels (6) had increased porphyrin synthesis from substrates glycine and succinyl CoA derived from GABA shunt pathway as indicated by increased ALA levels. The nair, autistic and civilizational disease group had features of Neanderthal metabolism as indicated by pyruvate dehydrogenase suppression.

There is an increased incidence of autism in the Nair community of Kerala with 68 percent of the autistic patient population of 1500 attending the Metabolic Centre belonging to this matrilineal community. The autistic population and the Nair population have the Neanderthal anthropometric phenotype with slanting forehead, large face, stubby nose, prominent mandibles, low 2D:4D ratio, large coarse trunk, macrocephaly and longer second toe as compared to big toe. Reports indicate that the autistic brain is larger and similar

in size to the Neanderthal brain. Neanderthal societies were matrilineal and matriarchal with female dominance. Autistic and Nair matrilinearity had also similarities with Neanderthal clusters. Matrilineal culture and matriarchy are seen in the Nair societies and they speak a Dravidian language. The language and culture of the matrilineal Nair community is similar to the Celtic, Basque, Berber and Scythian societies. Matrilineal Nair society with its high incidence of autism and Neanderthal anthropometric characteristics would represent fossilized remnants of the Neanderthal population along with the Celtic, Scythian, Basque and Berber societies.[2-17]

Autistic and Nair metabolonomic patterns had similarities with Neanderthals population. Neanderthals have a low efficient pyruvate dehydrogenase activity. The Neanderthals diet was rich in protein and fat and low in carbohydrate. Ketone body was used as the energy fuel and does not need the insulin receptor for metabolism. Therefore insulin resistance developed as a part of the Neanderthal diet and the Neanderthal phenotype is akin to the metabolic syndrome phenotype. As there was less need to metabolize glucose owing to an intake of high fat, high protein diet the enzyme pyruvate dehydrogenase would have evolved into a low efficiency system. Insulin resistance would have contributed to lipogenesis as a protective adaptation against the cold climate of the Ice age. Insulin resistance and ketogenic diet would have contributed to the longevity of the Neanderthal population. Pyruvate dehydrogenase deficiency leads to low acetyl CoA levels. This leads to a down regulated mevalonate pathway and low cholesterol synthesis. Low cholesterol values would have contributed to vitamin D deficiency in Neanderthals. Vitamin D deficiency and rickets would explain the skeletal abnormalities and macrocephaly of Neanderthals. Vitamin D deficiency would have led to fairer complexion of the Neanderthals in view of increased need of cutaneous UV ray absorption to promote increased vitamin D synthesis to correct its deficiency. Cholesterol

catabolizing endosymbiotic actinidic archaea has been described in systemic and neuropsychiatric disease from our laboratory. There is increased actinide dependent cytochrome F420 activity in autistic and normal Nair population. This indicates increased endosymbiotic archaeal growth which suppresses pyruvate dehydrogenase activity. Autistic and Nair metabolonomic patterns include low efficiency pyruvate dehydrogenase activity contributing to pyruvic acidemia. Pyruvate is not converted to acetyl CoA. Acetyl CoA deficiency results in mitochondrial oxidative phosphorylation defects and mitochondrial dysfunction. Energy is obtained from glycolysis and this leads to the genesis of the Warburg phenotype. The hexokinase activity was high and blood ATP levels were low. The cyto C activity in the blood was high indicating mitochondrial dysfunction. The pyruvate is channeled to the GABA shunt pathway to glutamate. Glutamate is acted upon by glutamate dehydrogenase generating ammonia which acts as a gasotransmitter modulating thalamo-cortico-thalamic GABA/NMDA function and consciousness. The GABA shunt pathway also generates succinyl CoA and glycine which are substrates for porphyrin synthesis contributing to porphyrinuria. Since glycine is utilized for porphyrin synthesis it is not available for cystathionine synthesis. This contributes to hyperhomocysteinemia and hypermethioninemia modulating genomic methylation patterns. Hyperhomocysteinemia, hyperammonemia and porphyrinuria are characteristic of autism. The low acetyl CoA leads to low cholesterol synthesis and low bile acid as well as vitamin D synthesis. Vitamin D and bile acids bind to the VDR producing immunosuppression and their deficiency contributes to the autoimmunity of autism. Vitamin D and bile acid deficiency can modulate neocortical development and contribute to autism. Low cholesterol levels can contribute to low sex hormone levels and less well defined gender phenotypes in autism.[2-17]

The increase in archaeal growth leads to an atavistic archaeal endosymbiotic colony with its own metabolic phenotype. The archaea are actinide dependent and use cholesterol as an energy substrate.[1] They have cholesterol ring oxidase activity generating pyruvate, side chain oxidase activity generating butyrate and propionate, aromatase activity generating the PAH ring and beta hydroxy steroid dehydrogenase activity generating the glycosidic digoxin and steroidal bile acids. The glycoside digoxin can regulate neural function, immune function and endocrine function. Digoxin can modulate cell death and cell proliferation. Digoxin can modulate intracellular calcium/magnesium ratios increasing cellular calcium and depleting cellular magnesium. The increase in intracellular calcium can modulate mitochondrial PT pore and its function. Digoxin by modulating sodium potassium ATPase can regulate cell membrane and nuclear membrane transport. Digoxin can modulate NFKB and produce immune activation. Digoxin can modulate G protein coupled and protein tyrosine kinase related neurotransmitter and endocrine receptors. Butyrate functions as a HDAC inhibitor regulating genomic function and also producing immunosuppression. Pyruvate is also immunosuppressive, regulates insulin secretion and functions as an antioxidant. PAH can modulate AHR receptor function regulating cell proliferation and immunity. Cholesterol oxidase activity can generate H_2O_2 and redox stress modulating cell function. The archaea can generate magnetite modulating magnetoperception and extrasensory perception. Thus the archaeal cholesterol catabolism can regulate genetic, immune, metabolic, endocrine and neural functions producing an atavistic phenotype. This atavistic archaeal colony functions as a new phenotype leading to cancer, degeneration, metabolic syndrome x, autoimmune disease, autism and schizophrenia. Climate change leads to global warming and increase in extremophilic archaeal growth. This leads onto autistic metabolic patterns and increased incidence of civilizational diseases. The human body is taken over by the atavistic archaeal colonial

phenotype. There is a body change, mind change and cultural change akin to climate change. This leads onto neanderthalisation of the human species.

The increase in archaeal growth and autistic metabolic patterns leads to autistic, cultural, neural and linguistic atavistic phenotypes. Low cholesterol values are characteristic of autistic brains. Low cholesterol levels can contribute to defective synaptogenesis as cholesterol is a trophic factor for synaptogenesis. This leads to reactive brain hypertrophy and neocortical dysfunction. Vitamin D deficiency can produce abnormalities in brain synaptogenesis and growth. Macrocephaly and large sized brains are seen in autism and Neanderthals. The Neanderthal have been postulated to have the APOBEC3G phenotype producing retroviral resistance as in Dravidian related Australian aboriginals. The Neanderthal hybrids are resistant to retroviral infections and have less of HERV load in the genome. The homo sapiens lack the APOBEC phenotype and are more susceptible to retroviral infections producing increased integration of HERV into the genome. HERV integration into the genome produces jumping genes and a dynamic genome. This dynamic genome is important in generation of complex synaptic networks and HLA phenotypes. This leads to the smaller size brain with increase in prefrontal cortex and autoimmunity in the homo sapiens unlike the Eurasian Neanderthal phenotype. The homo sapien brain with its prefrontal cortex dominance and smaller size is a consequence of HERV expression in contrast to the large sized Neanderthal brain with smaller prefrontal cortex which is induced by endosymbiotic archaeal over growth. Low cholesterol leads to low testosterone and estrogen levels and defective sex hormone modulation of brain function and growth. This would lead to defective stress response and sexual reproductive rates leading to eventual extinction of the Neanderthal population. Low testosterone levels and estrogen levels would lead to less defined asexual phenotypes, lack of male dominance, gender equality and matriarchal societies with group motherhood. This is the basis of the matriarchal cultural phenotype with lack of

male dominance. The low sex hormone levels would lead to low maturity rates seen in fossil specimens of characteristic of Neanderthals. Bile acids bind to the olfactory receptors and lead to limbic lobe stimulation and family bonding as well as bonding between individual mother and child. The group motherhood characteristic of matriarchy would be a reflection of low bile acid levels. The low bile acid levels leads to less family bonding. The porphyrins which are synthesized more in autism contribute to extrasensory perception. The porphyrins are dipolar molecules and can lead onto macroscopic quantal states. Extrasensory quantal perception is dominant in autism. The atavistic archaeal colony network has magnetite and actinide mediated magnetoperception in autism. Magnetoperception and porphyrins are involved in sensing of geomagnetic fields. The porphyrin and magnetite induced quantal perception can contribute to wave forms of the atavistic archaeal colony network generating macromolecular quantal states. This leads onto a feeling of oneness with nature and group. This leads onto group consciousness, group identity and group motherhood characteristic of Neanderthal clusters. There is no individual identity which is replaced with group identity. There is no family bonding which gets replaced with common motherhood. This fits in with the grandmother hypothesis with dominant females regulating the society. Neocortical function is defective due to defective synaptogenesis. Brain function is more intuitive than logical. There is more of emotional behavior than logical behavior. There is more of dreamy trance like spiritual states than wakeful states. The population lives in dreamy, hallucinatory state. Extrasensory perception contributes to spiritual experience in autism and Neanderthals. The conversion of ketone bodies derived from ketogenic diet to the neurotransmitter GABA and hydroxybutyric acid would have contributed to stimulation of inhibitory transmission in the brain and docile, spiritual behavior of Neanderthal societies. Neocortical dysfunction contributes to defective vocalization in Neanderthals. They also had a highly placed larynx contributing to

disordered symmetry between swallowing and breathing leading to evolution of linguistics characteristic of Dravidian language lacking quantal vowels. Language development and communication skills decline with more of gestural and extrasensory communication. Vocal language spoken and written becomes less and less widely used. The use of gestural and communicative music and dance becomes dominant in replacement to written and spoken speech. Symbolic gestural communicative forms and trances have been described in art forms of Kerala exemplified by Kathakali and Theyyams. This leads onto widespread generation of autistic brain phenotypes in the community which becomes more gender equal with its astereotyped asexual behavioural patterns. These phenomena can lead to globalization, loss of national identity, loss of sexual identity and universalization of behavior and thought.[2-17]

The autistic metabolonomic phenotype is also seen in cancer, autoimmune disease, degeneration, metabolic syndrome x and schizophrenia. This is due to a vagal neuropathy due to defective acetyl choline synthesis consequent to lack of substrate acetyl CoA. This also leads to sympathetic overactivity. Vagal neuropathy is associated with immune activation and autoimmune disease. Vagal neuropathy can contribute to insulin resistance and increased sympathetic activity to neoplastic transformation. The cholesterol synthetic defect leads to defective synaptogenesis seen in autism and schizophrenia. Cholesterol derived bile acid and vitamin D deficiency can contribute to schizophrenia and autism. Cholesterol is involved in contact inhibition and when the membranes are defective can lead to cell proliferation. Low cholesterol levels lead to low vitamin D and bile acid levels both of which bind to VDR producing immunosuppression. This can contribute to autoimmunity. Vitamin D deficiency can contribute to insulin resistance and metabolic syndrome phenotype in Neanderthals. Bile acids function as hormones regulating lipid and glucose metabolism and its deficiency can also contribute to syndrome x and insulin resistance. The Warburg phenotype

can also contribute to civilizational diseases. The increase in mitochondrial PT pore hexokinase can contribute to cell proliferation and cancer. The increase in GAPD (glyceraldehyde 3 phosphate dehydrogenase) can contribute to its ADP ribosylation and nuclear cell death. The increase in glycolysis can contribute to lymphocytes activation and autoimmune diseases. The MHC genes are of Neanderthal origin and autoimmunity is related to Neanderthal MHC alleles. Autoimmunity and antibrain antibodies are characteristic of autism. The phosphoglycerate, a glycolytic metabolite can be converted to serine a modulator of NMDA receptor and inhibitory neurotransmitter glycine. The increase in fructose 1,6 diphosphate results in its channeling to the pentose phosphate pathway generating NADPH stimulating NOX and redox stress contributing to disease. NOX is also involved in NMDA activity. Thus the generation of atavistic archaeal metabolic, immune and neuronal phenotype can contribute to civilizational diseases.

There is a mind change, linguistic change, cultural change, social change and spiritual change akin to climate change owing to increased archaeal growth as a consequence of global warming. The Neanderthal species evolved during periods of extreme climate change of the Ice age which led to increased extremophilic endosymbiotic archaeal growth. A similar extreme climate phenomenon of global warming is a feature of our current existence. This leads to increased extremophilic endosymbiotic archaeal growth and neanderthalisation of the population. Low cholesterol levels and low sex hormone levels would lead to asexual phenotypes and eventual population extinction. A new human species homo archaeax neanderthalis with its new anthropometric, metabolic, cultural, linguistic, neural, psychological and genetic atavistic phenotype is evolving.[2-17]

Table 1. *Incidence of autism in Nair, autistic and non-Nair population.*

Groups	Autism	Percentage
Nair	68 cases	68
Non-Nair	32 cases	32
Total	100	

Table 2. *Anthropometric features in Nair, autistic and non-Nair population.*

Groups	Neanderthal Anthropometric	Total	Percentage
Nair	72 cases	100	72
Non-Nair	21 cases	100	21
Autism	81 cases	100	81

Table 3. *Autistic metabolonomics.*

		Nair	Non-nair	Schizo	AD	MS
RBC Digoxin (ng/ml RBC Susp)	Mean	1.41	0.18	1.38	1.10	1.21
	± SD	0.23	0.05	0.26	0.08	0.21
Cytochrome F 420	Mean	4.00	0.00	4.00	4.00	4.00
	± SD	0.00	0.00	0.00	0.00	0.00
H_2O_2 (umol/ml RBC)	Mean	278.29	111.63	274.88	277.47	280.89
	± SD	7.74	5.40	8.73	10.90	11.25
NOX (OD diff/hr/ mgpro)	Mean	0.04	0.01	0.04	0.04	0.03
	± SD	0.01	0.00	0.01	0.01	0.01
TNF ALP (pg/ml)	Mean	78.63	9.29	78.23	79.65	80.18
	± SD	5.08	0.81	7.13	5.57	5.67
ALA (umol24)	Mean	63.50	3.86	66.16	67.32	64.00
	± SD	6.95	0.26	6.51	5.40	7.33
SE ATP (umol/dl)	Mean	2.24	0.02	1.26	2.06	1.63
	± SD	0.44	0.01	0.19	0.19	0.26
Cyto C (ng/ml)	Mean	12.39	1.21	11.58	11.94	11.81
	± SD	1.23	0.38	0.90	0.86	0.67
Lactate (mg/dl)	Mean	25.99	2.75	22.07	22.04	23.32
	± SD	8.10	0.41	1.06	0.64	1.10
Pyruvate (umol/l)	Mean	100.51	23.79	96.54	97.26	102.48
	± SD	12.32	2.51	9.96	8.26	13.20
RBC Hexokinase (ug glu phos/ hr/mgpro)	Mean	5.46	0.68	7.69	8.46	8.56
	± SD	2.83	0.23	3.40	3.63	4.75
ACOA (mg/dl)	Mean	2.51	16.49	2.51	2.19	2.03
	± SD	0.36	0.89	0.57	0.15	0.09
ACH (ug/ml)	Mean	38.57	91.98	48.52	42.84	39.99
	± SD	7.03	2.89	6.28	8.26	12.61
Glutamate (mg/dl)	Mean	3.19	0.16	3.41	3.53	3.58
	± SD	0.32	0.02	0.41	0.39	0.36
Se. Ammonia (ug/dl)	Mean	93.43	23.92	94.72	95.37	93.42
	± SD	4.85	3.38	3.28	4.66	3.69
Bile Acid (mg/ml)	Mean	25.68	140.40	22.45	26.26	24.12
	± SD	7.04	10.32	5.57	7.34	6.43
Cholesterol (mg/dl)	Mean	129.23	237.36	126.31	130.14	126.67
	± SD	10.03	38.07	6.93	6.64	5.70
Homocysteine (mg/dl)	Mean	37.49	9.18	31.50	31.75	38.39
	± SD	9.17	0.80	4.07	4.62	8.75

Table 3. *Continue.*

		Cancer	DM	Autism	F value	P value
RBC Digoxin (ng/ml RBC Susp)	Mean	1.27	1.35	1.19	60.288	< 0.001
	± SD	0.24	0.26	0.24		
Cytochrome F 420	Mean	4.00	4.00	4.00	0.001	< 0.001
	± SD	0.00	0.00	0.00		
H_2O_2 (umol/ml RBC)	Mean	278.19	280.89	274.52	713.569	< 0.001
	± SD	12.80	10.58	9.29		
NOX (OD diff/hr/ mgpro)	Mean	0.04	0.04	0.04	44.896	< 0.001
	± SD	0.01	0.01	0.01		
TNF ALP (pg/ml)	Mean	79.18	78.36	76.71	427.654	< 0.001
	± SD	5.88	6.68	5.25		
ALA (umol24)	Mean	67.67	64.72	68.16	295.467	< 0.001
	± SD	5.69	6.81	4.92		
SE ATP (umol/dl)	Mean	1.48	1.97	2.03	67.588	< 0.001
	± SD	0.32	0.11	0.12		
Cyto C (ng/ml)	Mean	13.00	12.95	12.48	445.772	< 0.001
	± SD	0.42	0.56	0.79		
Lactate (mg/dl)	Mean	22.20	25.56	21.95	162.945	< 0.001
	± SD	0.85	7.93	0.65		
Pyruvate (umol/l)	Mean	96.58	96.30	92.71	154.701	< 0.001
	± SD	8.75	10.33	8.43		
RBC Hexokinase (ug glu phos/ hr/mgpro)	Mean	7.82	7.05	6.95	18.187	< 0.001
	± SD	3.51	1.86	2.02		
ACOA (mg/dl)	Mean	2.34	2.17	2.42	1871.04	< 0.001
	± SD	0.43	0.40	0.41		
ACH (ug/ml)	Mean	42.51	41.31	50.61	116.901	< 0.001
	± SD	11.58	10.69	6.32		
Glutamate (mg/dl)	Mean	3.28	3.53	3.30	200.702	< 0.001
	± SD	0.39	0.44	0.32		
Se. Ammonia (ug/dl)	Mean	93.20	93.38	94.01	61.645	< 0.001
	± SD	4.46	7.76	5.00		
Bile Acid (mg/ml)	Mean	23.43	22.77	23.16	635.306	< 0.001
	± SD	6.03	4.94	5.78		
Cholesterol (mg/dl)	Mean	130.52	129.23	125.86	312.947	< 0.001
	± SD	8.01	5.97	7.79		
Homocysteine (mg/dl)	Mean	39.64	39.38	41.55	46.516	< 0.001
	± SD	9.21	7.00	7.62		

Table 4. *Cholesterol oxidase activity.*

		Nair	Non-nair	Schizo	AD	MS
CYT F420 % (Increase with Cerium)	Mean	23.46	4.48	23.24	23.12	22.12
	± SD	1.87	0.15	2.01	2.00	1.81
CYT F420 % (Decrease with Doxy+Cipro)	Mean	59.27	18.24	58.72	56.90	61.33
	± SD	8.86	0.66	7.08	6.94	9.82
PAH % change (Increase with Cerium)	Mean	22.67	4.45	23.01	23.26	22.83
	± SD	2.29	0.14	1.69	1.53	1.78
PAH % change (Decrease with Doxy+Cipro)	Mean	57.69	18.25	59.49	60.91	59.84
	± SD	5.29	0.72	4.30	7.59	7.62
Digoxin (ng/ml) (Increase with Cerium)	Mean	0.51	0.11	0.55	0.55	0.52
	± SD	0.05	0.00	0.06	0.03	0.03
Digoxin (ng/ml) (Decrease with Doxy+Cipro)	Mean	0.20	0.05	0.22	0.19	0.21
	± SD	0.03	0.00	0.04	0.04	0.03
Bile Acids % change (Increase with Cerium)	Mean	22.61	4.29	23.20	22.12	21.95
	± SD	2.22	0.18	1.87	2.19	2.11
Bile Acids % change (Decrease with Doxy+Cipro)	Mean	66.62	18.15	57.04	62.86	65.46
	± SD	4.99	0.58	4.27	6.28	5.79
Pyruvate % change (Increase with Cerium)	Mean	20.94	4.34	20.99	22.63	21.59
	± SD	1.54	0.21	1.46	0.88	1.23
Pyruvate % change (Decrease with Doxy+Cipro)	Mean	62.76	18.43	61.23	56.40	60.28
	± SD	8.52	0.82	9.73	8.59	9.22
H_2O_2 % (Increase with Cerium)	Mean	23.81	4.43	22.50	22.65	21.14
	± SD	1.19	0.19	1.66	2.48	1.20
H_2O_2 % (Decrease with Doxy+Cipro)	Mean	61.08	18.13	60.21	60.19	60.53
	± SD	7.38	0.63	7.42	6.98	4.70
Butyrate % (Increase with Cerium)	Mean	22.29	4.41	21.88	23.66	22.92
	± SD	1.33	0.15	1.19	1.67	2.14
Butyrate % (Decrease with Doxy+Cipro)	Mean	65.38	18.63	66.28	65.97	67.54
	± SD	3.62	0.12	3.60	3.36	3.65
Propionate % change (Increase with Cerium)	Mean	22.13	4.34	23.02	23.09	21.93
	± SD	2.14	0.15	1.65	1.81	2.29
Propionate % change (Decrease with Doxy+Cipro)	Mean	66.26	18.24	67.61	65.86	63.70
	± SD	3.93	0.37	2.77	4.27	5.63

Table 4. *Continue.*

		Cancer	DM	Autism	F value	P value
CYT F420 % (Increase with Cerium)	Mean	22.79	22.59	21.68	306.749	< 0.001
	± SD	2.13	1.86	1.90		
CYT F420 % (Decrease with Doxy+Cipro)	Mean	55.90	57.05	57.93	130.054	< 0.001
	± SD	7.29	8.45	9.64		
PAH % change (Increase with Cerium)	Mean	22.84	23.40	22.61	391.318	< 0.001
	± SD	1.42	1.55	1.42		
PAH % change (Decrease with Doxy+Cipro)	Mean	66.07	65.77	64.48	257.996	< 0.001
	± SD	3.78	5.27	6.90		
Digoxin (ng/ml) (Increase with Cerium)	Mean	0.54	0.47	0.53	135.116	< 0.001
	± SD	0.04	0.04	0.08		
Digoxin (ng/ml) (Decrease with Doxy+Cipro)	Mean	0.21	0.20	0.21	71.706	< 0.001
	± SD	0.04	0.03	0.04		
Bile Acids % change (Increase with Cerium)	Mean	22.98	22.87	22.21	290.441	< 0.001
	± SD	2.19	2.58	2.04		
Bile Acids % change (Decrease with Doxy+Cipro)	Mean	64.96	64.51	63.84	203.651	< 0.001
	± SD	5.64	5.93	6.16		
Pyruvate % change (Increase with Cerium)	Mean	21.19	20.67	21.91	321.255	< 0.001
	± SD	1.61	1.38	1.71		
Pyruvate % change (Decrease with Doxy+Cipro)	Mean	58.57	58.75	58.45	115.242	< 0.001
	± SD	7.47	8.12	6.66		
H_2O_2 % (Increase with Cerium)	Mean	23.35	23.27	23.52	380.721	< 0.001
	± SD	1.76	1.53	1.49		
H_2O_2 % (Decrease with Doxy+Cipro)	Mean	59.17	58.91	63.24	171.228	< 0.001
	± SD	3.33	6.09	7.36		
Butyrate % (Increase with Cerium)	Mean	23.81	24.10	22.76	403.394	< 0.001
	± SD	1.90	1.61	2.20		
Butyrate % (Decrease with Doxy+Cipro)	Mean	66.95	65.78	67.63	680.284	< 0.001
	± SD	3.67	4.43	3.52		
Propionate % change (Increase with Cerium)	Mean	23.12	22.73	22.79	348.867	< 0.001
	± SD	1.71	2.46	2.20		
Propionate % change (Decrease with Doxy+Cipro)	Mean	65.12	65.87	64.26	364.999	< 0.001
	± SD	5.58	4.35	6.02		

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Chapter 3

Endosymbiotic Actinidic Archaeal Mediated Warburg Phenotype Mediates Human Disease State

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.[1-4] The Warburg phenotype has been related to the pathogenesis of schizophrenia, malignancy, metabolic syndrome x, autoimmune disease and neuronal degeneration.[4] The possibility of Warburg phenotype induced by actinide based primitive organism like archaea with a mevalonate pathway and cholesterol catabolism was considered in this paper.[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 ℃ for 1 hour. The following estimations were carried out: - Cytochrome F420 and hexokinase.[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 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		130.054	
P value	< 0.001		< 0.001	

Table 2. *Effect of rutile and antibiotics on hexokinase.*

Group	Hexokinase % change (Increase with Rutile)		Hexokinase % change (Decrease with Doxy+Cipro)	
	Mean	± SD	Mean	± SD
Normal	4.21	0.16	18.56	0.76
Schizo	23.01	2.61	65.87	5.27
Seizure	23.33	1.79	62.50	5.56
AD	22.96	2.12	65.11	5.91
MS	22.81	1.91	63.47	5.81
NHL	22.53	2.41	64.29	5.44
DM	23.23	1.88	65.11	5.14
AIDS	21.11	2.25	64.20	5.38
CJD	22.47	2.17	65.97	4.62
Autism	22.88	1.87	65.45	5.08
EMF	21.66	1.94	67.03	5.97
F value	292.065		317.966	
P value	< 0.001		< 0.001	

Discussion

There was increase in cytochrome F420 indicating archaeal growth. 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, 16] The archaeal glycolytic hexokinase activity were increased. The part of the increased glycolytic hexokinase activity detected is human. The archaea can undergo magnetite and calcium carbonate mineralization and can exist as calcified nanoforms.[17]

Archaea can induce the host AKT PI3K, AMPK, HIF alpha and NFKB producing the Warburg metabolic phenotype.[18] The increased glycolytic hexokinase activity indicates the generation of the Warburg phenotype. The generation of the Warburg phenotype is due to activation of HIF alpha. This stimulates anaerobic glycolysis, inhibits pyruvate dehydrogenase, inhibits mitochondrial oxidative phosphorylation, stimulates heme oxygenase, stimulates VEGF and activates nitric oxide synthase. This can lead to increased cell proliferation and malignant transformation. The mitochondrial PT pore hexokinase is increased leading onto cell proliferation. There is induction of glycolysis, inhibition of PDH activity and mitochondrial dysfunction resulting in inefficient energetics and metabolic syndrome. The archaea and viroid generated cytokines can lead to TNF alpha induced insulin resistance and metabolic syndrome x. The increase in glycolysis can activate glyceraldehyde 3 phosphate dehydrogenase which gets translocated to the nucleus after polyadenylation. The PARP enzyme is activated by glycolysis mediated redox stress. 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.[18]

The increase in glycolysis activates the enzyme fructose 1,6 diphosphatase which activates the pentose phosphate pathway liberating NADPH. This increases NOX activity generating free radical stress and H_2O_2. Free radical stress is related to insulin resistance and metabolic syndrome x. Free radicals can activate NFKB producing immune activation and autoimmune disease. Free radicals can open the mitochondrial PT pore, produce release of cyto C and activate the caspase cascade. This produces cell death and neuronal degeneration. The free radicals can activate NMDA receptor and induce the enzyme GAD generating GABA. This activates the NMDA/GABA thalamo-cortico-thalamic pathway mediating conscious perception. Increased free radical generation can also initiate schizophrenia. Free radicals can also produce oncogene activation and malignant transformation. Free radicals can produce HDAC inhibition and HERV generation. The encapsulation of HERV particles in phospholipids vesicles can mediate the generation of the acquired immunodeficiency syndrome. Free radicals can also promote atherogenesis.[18]

The lymphocytes depend on glycolysis for its energy needs. The increase in glycolysis owing to the induction of Warburg phenotype can lead to immune activation. Immune activation can lead to autoimmune disease. TNF alpha can activate the NMDA receptor leading to glutamate excitotoxicity and neuronal degeneration. TNF alpha activating NMDA receptor can contribute to schizophrenia. TNF alpha can induce expression of HERV particles contributing to generation of acquired immunodeficiency syndrome. Immune activation has also been related to malignant transformation mediated by NFKB. TNF alpha can also act upon the insulin receptor producing insulin resistance.

NOX activation consequent to the generation of the Warburg phenotype also activates the insulin receptor. Thus there is a hyperinsulinemic state leading on to metabolic syndrome x.[18]

The inhibition of pyruvate dehydrogenase results in defective formation of acetyl CoA. This results in defective N acetylation of lysyl residues of proteins producing defective protein confirmation. There are nearly 3000 acetylated proteins and defects in protein acetylation can lead to defective function. Thus the inhibition of PDH can modulate proteonomic function. Acetate is also a HDAC inhibitor. Acetyl CoA is also required for histone acetylation. HDAC inhibition and histone acetylation can modulate chromatin structure and gene expression. Thus PDH inhibition can modulate genomic expression.

The Warburg phenotype results in upregulation of glycolysis and the immune system depends upon glycolysis for its energetics. The immune system is regulated by the HLA system and the HLA genes are of neanderthalic origin. The mitochondria is of homo sapiens origin and the cytosolic glycolytic pathway is of Neanderthal origin. This leads to autoimmunity against glycolytic enzymes. Antiglycolytic enzymes autoantibodies in the hybrid population are common in multiple sclerosis, lupus, autoimmune encephalitis and antibasal ganglia antibody disease.

Thus the induction of the Warburg phenotype can lead to malignancy, autoimmune disease, metabolic syndrome x, neuropsychiatric disease and neuronal degeneration. The Warburg phenotype leads to inhibition of pyruvate dehydrogenase and accumulation of pyruvate. 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. 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 further induction of the Warburg phenotype.[18]

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