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A Neo-Neanderthalisation Related Porphyrin Metabolic Dysfunction Underlies the 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. Increased actinidic archaeal growth leads to neanderthalisation of homo sapiens and generation of Neanderthal metabolonomics. Neanderthal metabolonomics results in porphyria. 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] Neo-neanderthalisation porphyric syndrome underlies this disorder.

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^oC 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 cytoC 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

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
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 P value < 0.001		F value 130.054 P value < 0.001		F value 391.318 P value < 0.001		F value 257.996 P value < 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 P value < 0.001		F value 356.621 P value < 0.001		F value 427.828 P value < 0.001		F value 654.453 P value < 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 P value < 0.001		F value 71.706 P value < 0.001		F value 372.716 P value < 0.001		F value 556.411 P value < 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 P value < 0.001		F value 680.284 P value < 0.001		F value 348.867 P value < 0.001		F value 364.999 P value < 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 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 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 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	

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. *RBC Digoxin (ng/ml RBC Susp).*

Group	Mean	± SD
NO/BHCD	0.58	0.07
RHCD	1.41	0.23
LHCD	0.18	0.05
Migraine	1.38	0.26
Bronchial asthma	1.23	0.26
Hypertension/CAN	1.34	0.31
IBS	1.10	0.08
IBD	1.21	0.21
PUD	1.50	0.33
NPH with HE	1.26	0.23
Panic syndrome	1.27	0.24
CFS	1.35	0.26
CAD	1.22	0.16
CVA	1.33	0.27
Polyendocrine failure	1.31	0.24
Sexual dysautonomia	1.48	0.27
F value	60.288	
P value	< 0.001	

Table 2. *Cytochrome F 420.*

Group	Mean	± SD
NO/BHCD	1.00	0.00
RHCD	4.00	0.00
LHCD	0.00	0.00
Migraine	4.00	0.00
Bronchial asthma	4.00	0.00
Hypertension/CAN	4.00	0.00
IBS	4.00	0.00
IBD	4.00	0.00
PUD	4.00	0.00
NPH with HE	4.00	0.00
Panic syndrome	4.00	0.00
CFS	4.00	0.00
CAD	4.00	0.00
CVA	4.00	0.00
Polyendocrine failure	4.00	0.00
Sexual dysautonomia	4.00	0.00
F value	0.001	
P value	< 0.001	

Table 3. *HERV RNA (ug/ml).*

Group	**Mean**	**± SD**
NO/BHCD	17.75	0.72
RHCD	55.17	5.85
LHCD	8.70	0.90
Migraine	51.17	3.65
Bronchial asthma	50.04	3.91
Hypertension/CAN	51.16	7.78
IBS	51.56	3.69
IBD	47.90	6.99
PUD	48.20	5.53
NPH with HE	51.08	5.24
Panic syndrome	51.57	2.66
CFS	51.98	5.05
CAD	50.00	5.91
CVA	51.06	4.83
Polyendocrine failure	50.15	6.96
Sexual dysautonomia	49.85	6.40
F value	194.418	
P value	< 0.001	

Table 4. *H_2O_2 (umol/ml RBC).*

Group	**Mean**	**± SD**
NO/BHCD	177.43	6.71
RHCD	278.29	7.74
LHCD	111.63	5.40
Migraine	274.88	8.73
Bronchial asthma	278.90	11.20
Hypertension/CAN	295.37	3.78
IBS	277.47	10.90
IBD	280.89	11.25
PUD	278.59	11.51
NPH with HE	283.39	10.67
Panic syndrome	278.19	12.80
CFS	280.89	10.58
CAD	280.89	13.79
CVA	287.33	9.47
Polyendocrine failure	278.58	12.72
Sexual dysautonomia	286.16	10.90
F value	713.569	
P value	< 0.001	

Table 5. *NOX (OD diff/hr/mgpro).*

Group	**Mean**	**± SD**
NO/BHCD	0.012	0.001
RHCD	0.036	0.008
LHCD	0.007	0.001
Migraine	0.036	0.009
Bronchial asthma	0.038	0.007
Hypertension/CAN	0.035	0.011
IBS	0.036	0.007
IBD	0.034	0.009
PUD	0.038	0.008
NPH with HE	0.041	0.006
Panic syndrome	0.038	0.007
CFS	0.041	0.005
CAD	0.038	0.009
CVA	0.037	0.007
Polyendocrine failure	0.039	0.010
Sexual dysautonomia	0.039	0.006
F value	44.896	
P value	< 0.001	

Table 6. *TNF ALP (pg/ml).*

Group	**Mean**	**± SD**
NO/BHCD	17.94	0.59
RHCD	78.63	5.08
LHCD	9.29	0.81
Migraine	78.23	7.13
Bronchial asthma	79.28	4.55
Hypertension/CAN	82.13	3.97
IBS	79.65	5.57
IBD	80.18	5.67
PUD	81.03	6.22
NPH with HE	77.98	5.68
Panic syndrome	79.18	5.88
CFS	78.36	6.68
CAD	78.15	3.72
CVA	77.59	5.24
Polyendocrine failure	79.17	5.88
Sexual dysautonomia	80.41	5.70
F value	427.654	
P value	< 0.001	

Table 7. *ALA (umol24).*

Group	Mean	+ SD
NO/BHCD	15.44	0.50
RHCD	63.50	6.95
LHCD	3.86	0.26
Migraine	66.16	6.51
Bronchial asthma	68.28	6.02
Hypertension/CAN	67.30	5.98
IBS	67.32	5.40
IBD	64.00	7.33
PUD	65.01	5.42
NPH with HE	63.21	6.55
Panic syndrome	67.67	5.69
CFS	64.72	6.81
CAD	66.66	7.77
CVA	69.02	4.86
Polyendocrine failure	67.78	4.41
Sexual dysautonomia	66.99	3.71
F value	295.467	
P value	< 0.001	

Table 8. *PBG (umol24).*

Group	Mean	+ SD
NO/BHCD	20.82	1.19
RHCD	42.20	8.50
LHCD	12.11	1.34
Migraine	42.50	3.23
Bronchial asthma	46.54	4.55
Hypertension/CAN	47.25	4.19
IBS	49.83	3.45
IBD	46.85	3.49
PUD	48.55	3.81
NPH with HE	47.17	4.86
Panic syndrome	46.84	4.43
CFS	48.15	3.36
CAD	47.00	3.81
CVA	46.33	4.01
Polyendocrine failure	48.03	3.64
Sexual dysautonomia	47.94	5.33
F value	183.296	
P value	< 0.001	

Table 9. *UROPORPHYRIN (nmol24).*

Group	**Mean**	**+ SD**
NO/BHCD	50.18	3.54
RHCD	250.28	23.43
LHCD	9.51	1.19
Migraine	267.81	64.05
Bronchial asthma	290.44	57.65
Hypertension/CAN	286.84	24.18
IBS	259.61	33.18
IBD	277.36	15.48
PUD	294.51	58.62
NPH with HE	310.25	40.44
Panic syndrome	304.19	14.16
CFS	285.46	29.46
CAD	314.01	17.82
CVA	320.85	24.73
Polyendocrine failure	306.61	22.47
Sexual dysautonomia	317.92	29.63
F value	160.533	
P value	< 0.001	

Table 10. *COPROPORPHYRIN (nmol/24).*

Group	**Mean**	**+ SD**
NO/BHCD	137.94	4.75
RHCD	389.01	54.11
LHCD	64.33	13.09
Migraine	401.49	50.73
Bronchial asthma	436.71	52.95
Hypertension/CAN	432.22	50.11
IBS	433.17	45.61
IBD	440.35	25.34
PUD	447.39	39.84
NPH with HE	495.98	39.11
Panic syndrome	479.35	58.86
CFS	422.27	33.86
CAD	426.14	24.28
CVA	402.16	33.80
Polyendocrine failure	429.72	24.97
Sexual dysautonomia	429.24	18.29
F value	279.759	
P value	< 0.001	

Table 11. *PROTOPORPHYRIN (Ab unit).*

Group	Mean	± SD
NO/BHCD	10.35	0.38
RHCD	42.46	6.36
LHCD	2.64	0.42
Migraine	44.30	2.66
Bronchial asthma	49.59	1.70
Hypertension/CAN	49.36	4.18
IBS	49.68	3.30
IBD	50.81	3.21
PUD	52.94	3.67
NPH with HE	54.80	4.04
Panic syndrome	53.73	5.34
CFS	49.80	4.01
CAD	49.51	2.27
CVA	46.74	4.28
Polyendocrine failure	49.32	5.13
Sexual dysautonomia	50.02	4.58
F value	424.198	
P value	< 0.001	

Table 12. *HEME (uM).*

Group	Mean	± SD
NO/BHCD	30.27	0.81
RHCD	12.47	2.82
LHCD	50.55	1.07
Migraine	12.82	2.40
Bronchial asthma	13.03	0.70
Hypertension/CAN	11.81	0.80
IBS	12.09	1.12
IBD	11.87	1.84
PUD	12.95	1.53
NPH with HE	11.76	1.37
Panic syndrome	13.68	1.67
CFS	12.83	2.07
CAD	11.39	1.10
CVA	11.26	0.95
Polyendocrine failure	11.60	1.23
Sexual dysautonomia	11.76	1.32
F value	1472.05	
P value	< 0.001	

Table 13. *Bilirubin (mg/dl).*

Group	Mean	± SD
NO/BHCD	0.55	0.02
RHCD	1.70	0.20
LHCD	0.21	0.00
Migraine	1.74	0.08
Bronchial asthma	1.84	0.07
Hypertension/CAN	1.83	0.09
IBS	1.77	0.13
IBD	1.81	0.10
PUD	1.82	0.08
NPH with HE	1.84	0.08
Panic syndrome	1.76	0.11
CFS	1.77	0.19
CAD	1.75	0.12
CVA	1.82	0.10
Polyendocrine failure	1.79	0.08
Sexual dysautonomia	1.82	0.09
F value	370.517	
P value	< 0.001	

Table 14. *Biliverdin (Ab unit).*

Group	Mean	± SD
NO/BHCD	0.030	0.001
RHCD	0.067	0.011
LHCD	0.017	0.001
Migraine	0.073	0.013
Bronchial asthma	0.070	0.015
Hypertension/CAN	0.071	0.014
IBS	0.073	0.016
IBD	0.079	0.007
PUD	0.061	0.006
NPH with HE	0.077	0.011
Panic syndrome	0.073	0.012
CFS	0.067	0.014
CAD	0.080	0.007
CVA	0.079	0.009
Polyendocrine failure	0.072	0.013
Sexual dysautonomia	0.066	0.009
F value	59.963	
P value	< 0.001	

Table 15. ATP Synthase (umol/gHb).

Group	Mean	± SD
NO/BHCD	0.36	0.13
RHCD	2.73	0.94
LHCD	0.09	0.01
Migraine	2.66	0.58
Bronchial asthma	3.09	0.65
Hypertension/CAN	3.34	0.84
IBS	3.34	0.75
IBD	3.05	0.52
PUD	2.85	0.34
NPH with HE	3.01	0.55
Panic syndrome	2.70	0.62
CFS	3.19	0.89
CAD	2.99	0.65
CVA	2.98	0.78
Polyendocrine failure	3.29	0.63
Sexual dysautonomia	3.21	0.95
F value	54.754	
P value	< 0.001	

Table 16. SE ATP (umol/dl).

Group	Mean	± SD
NO/BHCD	0.42	0.11
RHCD	2.24	0.44
LHCD	0.02	0.01
Migraine	1.26	0.19
Bronchial asthma	1.66	0.56
Hypertension/CAN	1.27	0.26
IBS	2.06	0.19
IBD	1.63	0.26
PUD	1.59	0.22
NPH with HE	1.73	0.26
Panic syndrome	1.48	0.32
CFS	1.97	0.11
CAD	1.57	0.37
CVA	1.49	0.27
Polyendocrine failure	1.59	0.38
Sexual dysautonomia	1.69	0.43
F value	67.588	
P value	< 0.001	

Table 17. *Cyto C (ng/ml).*

Group	Mean	± SD
NO/BHCD	2.79	0.28
RHCD	12.39	1.23
LHCD	1.21	0.38
Migraine	11.58	0.90
Bronchial asthma	12.06	1.09
Hypertension/CAN	12.65	1.06
IBS	11.94	0.86
IBD	11.81	0.67
PUD	11.73	0.56
NPH with HE	11.91	0.49
Panic syndrome	13.00	0.42
CFS	12.95	0.56
CAD	11.51	0.47
CVA	12.74	0.80
Polyendocrine failure	12.29	0.89
Sexual dysautonomia	12.19	1.22
F value	445.772	
P value	< 0.001	

Table 18. *Lactate (mg/dl).*

Group	Mean	± SD
NO/BHCD	7.38	0.31
RHCD	25.99	8.10
LHCD	2.75	0.41
Migraine	22.07	1.06
Bronchial asthma	21.78	0.58
Hypertension/CAN	24.28	1.69
IBS	22.04	0.64
IBD	23.32	1.10
PUD	23.06	1.49
NPH with HE	22.83	1.24
Panic syndrome	22.20	0.85
CFS	25.56	7.93
CAD	22.83	0.82
CVA	23.03	1.26
Polyendocrine failure	24.87	4.14
Sexual dysautonomia	23.02	1.61
F value	162.945	
P value	< 0.001	

Table 19. *Pyruvate (umol/l).*

Group	**Mean**	**+ SD**
NO/BHCD	40.51	1.42
RHCD	100.51	12.32
LHCD	23.79	2.51
Migraine	96.54	9.96
Bronchial asthma	90.46	8.30
Hypertension/CAN	95.44	12.04
IBS	97.26	8.26
IBD	102.48	13.20
PUD	100.51	9.79
NPH with HE	95.81	12.18
Panic syndrome	96.58	8.75
CFS	96.30	10.33
CAD	97.29	12.45
CVA	103.25	9.49
Polyendocrine failure	95.55	7.20
Sexual dysautonomia	96.50	5.93
F value	154.701	
P value	< 0.001	

Table 20. *RBC Hexokinase (ug glu phos/hr/mgpro).*

Group	**Mean**	**+ SD**
NO/BHCD	1.66	0.45
RHCD	5.46	2.83
LHCD	0.68	0.23
Migraine	7.69	3.40
Bronchial asthma	6.29	1.73
Hypertension/CAN	9.30	3.98
IBS	8.46	3.63
IBD	8.56	4.75
PUD	8.02	3.01
NPH with HE	7.41	4.22
Panic syndrome	7.82	3.51
CFS	7.05	1.86
CAD	8.88	3.09
CVA	7.87	2.72
Polyendocrine failure	9.84	2.43
Sexual dysautonomia	8.81	4.26
F value	18.187	
P value	< 0.001	

Table 21. *ACOA (mg/dl).*

Group	Mean	+ SD
NO/BHCD	8.75	0.38
RHCD	2.51	0.36
LHCD	16.49	0.89
Migraine	2.51	0.57
Bronchial asthma	2.15	0.22
Hypertension/CAN	1.95	0.06
IBS	2.19	0.15
IBD	2.03	0.09
PUD	2.54	0.38
NPH with HE	2.30	0.26
Panic syndrome	2.34	0.43
CFS	2.17	0.40
CAD	2.37	0.44
CVA	2.25	0.44
Polyendocrine failure	2.11	0.19
Sexual dysautonomia	2.10	0.27
F value	1871.04	
P value	< 0.001	

Table 22. *ACH (ug/ml).*

Group	Mean	+ SD
NO/BHCD	75.11	2.96
RHCD	38.57	7.03
LHCD	91.98	2.89
Migraine	48.52	6.28
Bronchial asthma	33.27	5.99
Hypertension/CAN	35.02	5.85
IBS	42.84	8.26
IBD	39.99	12.61
PUD	49.30	7.26
NPH with HE	50.58	3.82
Panic syndrome	42.51	11.58
CFS	41.31	10.69
CAD	49.19	6.86
CVA	37.45	7.93
Polyendocrine failure	38.40	7.74
Sexual dysautonomia	34.97	4.24
F value	116.901	
P value	< 0.001	

Table 23. *Glutamate (mg/dl).*

Group	Mean	+ SD
NO/BHCD	0.65	0.03
RHCD	3.19	0.32
LHCD	0.16	0.02
Migraine	3.41	0.41
Bronchial asthma	3.67	0.38
Hypertension/CAN	3.14	0.32
IBS	3.53	0.39
IBD	3.58	0.36
PUD	3.37	0.38
NPH with HE	3.48	0.46
Panic syndrome	3.28	0.39
CFS	3.53	0.44
CAD	3.61	0.28
CVA	3.31	0.43
Polyendocrine failure	3.45	0.49
Sexual dysautonomia	3.94	0.22
F value	200.702	
P value	< 0.001	

Table 24. *Se. Ammonia (ug/dl).*

Group	Mean	+ SD
NO/BHCD	50.60	1.42
RHCD	93.43	4.85
LHCD	23.92	3.38
Migraine	94.72	3.28
Bronchial asthma	95.61	7.88
Hypertension/CAN	94.60	8.52
IBS	95.37	4.66
IBD	93.42	3.69
PUD	101.18	17.06
NPH with HE	91.62	3.24
Panic syndrome	93.20	4.46
CFS	93.38	7.76
CAD	93.93	4.86
CVA	103.18	27.27
Polyendocrine failure	92.47	3.97
Sexual dysautonomia	93.13	5.79
F value	61.645	
P value	< 0.001	

Table 25. *HMG Co A (HMG CoA/MEV).*

Group	Mean	± SD
NO/BHCD	1.70	0.07
RHCD	1.16	0.10
LHCD	2.21	0.39
Migraine	1.11	0.08
Bronchial asthma	1.14	0.07
Hypertension/CAN	1.08	0.13
IBS	1.10	0.07
IBD	1.13	0.08
PUD	1.14	0.07
NPH with HE	1.12	0.10
Panic syndrome	1.10	0.09
CFS	1.09	0.12
CAD	1.07	0.12
CVA	1.05	0.09
Polyendocrine failure	1.08	0.11
Sexual dysautonomia	1.09	0.12
F value	159.963	
P value	< 0.001	

Table 26. *Bile Acid (mg/ml).*

Group	Mean	± SD
NO/BHCD	79.99	3.36
RHCD	25.68	7.04
LHCD	140.40	10.32
Migraine	22.45	5.57
Bronchial asthma	22.98	5.19
Hypertension/CAN	28.93	4.93
IBS	26.26	7.34
IBD	24.12	6.43
PUD	19.62	1.97
NPH with HE	23.45	5.01
Panic syndrome	23.43	6.03
CFS	22.77	4.94
CAD	24.55	6.26
CVA	22.39	3.35
Polyendocrine failure	23.28	5.81
Sexual dysautonomia	21.26	4.81
F value	635.306	
P value	< 0.001	

Abbreviations

BHCD: 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 autooxidation 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 autooxidation 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 channeling 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 channeling 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. Protoporphyrine 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 group 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 thalamocorticothalamic pathway mediating conscious perception. Porphyrin photo-oxidation 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 thalamocorticothalamic 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 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. 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 cytoC 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 macrosopic 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 thalamocorticothalamic 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 H2S 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 neo-neanderthalisation related porphyrin metabolic dysfunction related CVS-pulmonary-GIT dysautonomia, coronary/cerebral microangiopathy, polyendocrine failure and chronic fatigue/panic syndrome complex is described. Increased actinidic archaeal growth leads to neanderthalisation of homo sapiens and generation of Neanderthal metabolonomics. Neanderthal metabolonomics results in porphyria. Neo-neanderthalisation porphyric syndrome underlies this disorder.

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