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Porphyrins Regulate the Metabolic and Endocrine System: Role in Generation of Warburg Phenotype, Endogenous Digoxin Synthesis and Metabolic Syndrome X with Type 2 Diabetes Mellitus

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Abstract

Objectives: Actinidic archaea have been related to the pathogenesis of metabolic syndrome x. An actinide dependent shadow biosphere of archaea and viroids has been described in metabolic syndrome x with type 2 diabetes mellitus. 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. Porphyrins have been related to metabolic syndrome x and type 2 diabetes mellitus. The role of archaeal porphyrins in regulation of cell functions, metabolism and endocrine function is discussed. Porphyrins play a key role in the generation of the Warburg phenotype, endogenous digoxin synthesis and metabolic syndrome x with type 2 diabetes mellitus.

Methodology: The following groups were included in the study: - metabolic syndrome x with cerebrovascular thrombosis and coronary artery disease. There were 10 patients in each group and each patient had an age and sex matched healthy control selected randomly from the general population. The blood samples were drawn in the fasting state before treatment was initiated. Plasma from fasting heparinised blood was used and the experimental protocol was as follows (I) Plasma + phosphate buffered saline, (II) same as I + cholesterol substrate, (III) same as II + rutile 0.1 mg/ml, (IV) same as II + ciprofloxacine and doxycycline each in a concentration of 1 mg/ml. The following estimations were carried out: - Cytochrome F420, free RNA, free DNA, polycyclic aromatic hydrocarbon, hydrogen peroxide, pyruvate, ammonia, glutamate, succinate, glycine, delta aminolevulinic acid and digoxin. The study also involved estimating the following parameters in the patient population- hexokinase, porphyrins, pyruvate, glutamate, ammonia, succinic acid, serine, glycine, HMG CoA reductase, cytochrome C, blood ATP and heme oxygenase.

Results: Plasma of control subjects showed increased levels of the above mentioned parameters with after incubation for 1 hour and addition of cholesterol substrate resulted in still further significant increase in these parameters. The plasma of patients showed similar results but the extent of increase was more. The addition of antibiotics to the control plasma caused a decrease in all the parameters while addition of rutile increased their levels. The addition of antibiotics and rutile to the patient's plasma produced the same changes but the extent of change was more in patient's sera as compared to controls. 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 had increased heme oxygenase activity, increased serine, glycine, succinic acid and porphyrins. The hexokinase activity was high. The pyruvate, glutamate, ammonia, GABA and succinic acid levels were elevated indicating blockade of PDH activity, and operation of the GABA shunt pathway. 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. The HMG CoA reductase activity was high indicating cholesterol synthesis. The RHCD population had values similar to the patient population.

The LHCD population had opposite values.

Conclusion: An actinide dependent shadow biosphere of archaea and viroids in metabolic syndrome x with coronary and cerebrovascular diseases. The porphyrins can contribute to the pathogenesis of metabolic syndrome x with coronary and cerebrovascular diseases. 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. Porphyrins can regulate hemispheric dominance. The archaeal porphyrins functions as key regulatory molecules with mitochondrial benzodiazepine receptors playing an important role.

Key words: Actinide; Archaea; Porphyrins; GABA shunt; Peripheral benzodiazepine receptor; Delta aminolevulinic acid; Metabolic syndrome x; Type 2 diabetes mellitus; Coronary artery disease; Cerebrovascular disease

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INTRODUCTION

Actinidic archaea have been related to the pathogenesis of metabolic syndrome x. An actinide dependent shadow biosphere of archaea and viroids has been described in metabolic syndrome x with type 2 diabetes mellitus. 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. Porphyrins have been related to metabolic syndrome x and type 2 diabetes mellitus. The role of archaeal porphyrins in regulation of cell functions, metabolism and endocrine function is discussed. Porphyrins play a key role in the generation of the Warburg phenotype, endogenous digoxin synthesis and metabolic syndrome x with type 2 diabetes mellitus.[1-5]

MATERIALS AND METHODS

The following groups were included in the study: - metabolic syndrome x with cerebrovascular thrombosis and coronary artery disease. There were 10 patients in each group and each patient had an age and sex matched healthy control selected randomly from the general population. There were also 10 normal population samples with right hemispheric, left hemispheric and bihemispheric dominance selected for the study. 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^{o}C 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 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
DM	22.59	1.86	57.05	8.45	23.40	1.55	65.77	5.27
CVA	22.29	1.66	59.02	7.50	23.23	1.97	65.89	5.05
CAD	22.06	1.61	57.81	6.04	23.46	1.91	61.56	4.61
	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
DM	23.01	1.67	65.35	3.56	23.33	1.86	66.46	3.65
CVA	22.29	2.05	58.70	7.34	22.29	2.05	67.03	5.97
CAD	22.56	2.46	62.70	4.53	23.32	1.74	65.67	4.16
	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
DM	0.47	0.04	0.202	0.025	22.87	1.84	66.31	3.68
CVA	0.53	0.06	0.212	0.045	23.17	1.88	68.53	2.65
CAD	0.53	0.08	0.205	0.041	23.20	1.57	66.65	4.26
	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
DM	23.70	1.75	68.06	3.52	23.81	1.49	64.89	6.01
CVA	23.66	1.67	65.97	3.36	23.09	1.81	65.86	4.27
CAD	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
DM	20.67	1.38	58.75	8.12	23.23	1.88	65.11	5.14
CVA	22.29	2.05	62.37	5.05	21.66	1.94	67.03	5.97
CAD	21.07	1.79	63.90	7.13	22.47	2.17	65.97	4.62
	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
DM	23.27	1.53	58.91	6.09	22.87	1.84	66.31	3.68
CVA	23.29	1.67	60.52	5.38	22.29	2.05	61.91	7.56
CAD	23.32	1.71	63.15	7.62	23.45	1.79	66.32	3.63
	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	

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
DM	1.35	0.26
CAD	1.22	0.16
CVA	1.33	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
DM	4.00	0.00
CAD	4.00	0.00
CVA	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
DM	51.98	5.05
CAD	50.00	5.91
CVA	51.06	4.83
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
DM	280.89	10.58
CAD	280.89	13.79
CVA	287.33	9.47
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
DM	0.041	0.005
CAD	0.038	0.009
CVA	0.037	0.007
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
DM	78.36	6.68
CAD	78.15	3.72
CVA	77.59	5.24
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
DM	64.72	6.81
CAD	66.66	7.77
CVA	69.02	4.86
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
DM	48.15	3.36
CAD	47.00	3.81
CVA	46.33	4.01
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
DM	285.46	29.46
CAD	314.01	17.82
CVA	320.85	24.73
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
DM	422.27	33.86
CAD	426.14	24.28
CVA	402.16	33.80
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
DM	49.80	4.01
CAD	49.51	2.27
CVA	46.74	4.28
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
DM	12.83	2.07
CAD	11.39	1.10
CVA	11.26	0.95
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
DM	1.77	0.19
CAD	1.75	0.12
CVA	1.82	0.10
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
DM	0.067	0.014
CAD	0.080	0.007
CVA	0.079	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
DM	3.19	0.89
CAD	2.99	0.65
CVA	2.98	0.78
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
DM	1.97	0.11
CAD	1.57	0.37
CVA	1.49	0.27
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
DM	12.95	0.56
CAD	11.51	0.47
CVA	12.74	0.80
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
DM	25.56	7.93
CAD	22.83	0.82
CVA	23.03	1.26
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
DM	96.30	10.33
CAD	97.29	12.45
CVA	103.25	9.49
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
DM	7.05	1.86
CAD	8.88	3.09
CVA	7.87	2.72
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
DM	2.17	0.40
CAD	2.37	0.44
CVA	2.25	0.44
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
DM	41.31	10.69
CAD	49.19	6.86
CVA	37.45	7.93
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
DM	3.53	0.44
CAD	3.61	0.28
CVA	3.31	0.43
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
DM	93.38	7.76
CAD	93.93	4.86
CVA	103.18	27.27
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
DM	1.09	0.12
CAD	1.07	0.12
CVA	1.05	0.09
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
DM	22.77	4.94
CAD	24.55	6.26
CVA	22.39	3.35
F value	635.306	
P value	< 0.001	

Abbreviations:
NO/BHCD: Normal/ Bi-hemispheric chemical dominance
RHCD: Right hemispheric chemical dominance
LHCD: Left hemispheric chemical dominance
DM: Diabetes mellitus type 2
CAD: Coronary artery disease
CVA: Cerebrovascular disease-thrombotic

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 possibility of Warburg phenotype induced by actinide based primitive organism like archaea with a mevalonate pathway and cholesterol catabolism was considered in this paper. 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 metabolic syndrome x, coronary artery disease and cerebrovascular disease. Mitochondrial dysfunction contributes to metabolic syndrome x, coronary artery disease and cerebrovascular disease.

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 neuroimmunoendocrine system. Thus the elevated digoxin synthesis noted in metabolic syndrome x with CAD and CVA is due to alteration in porphyrin synthesis. Hyperdigoxinemia is related to metabolic syndrome x with CAD and CVA. Porphyrins can combine with membranes modulating membrane 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 function. Porphyrin interpolating with DNA can alter transcription and generate HERV expression. 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. The glutathione peroxidase is dysfunctional and the glutathione system of free radical scavenging does not function. The cytochrome P450 enzymes involved in steroid and bile acid synthesis have reduced activity leading to steroid-cortisol and sex hormones as well as bile acid deficiency states. Thus porphyrin metabolism can regulate cortisol, testosterone and estrogen levels. Thyroid peroxidase is a heme enzyme. Porphyrin metabolism related heme deficiency can produce defects in thyroxine synthesis. Thus porphyrine metabolic defect can produce adrenal, testes, ovary and thyroid dysfunction as well as contributing to an insulin resistance

state. Ovarian, testicular and thyroid dysfunction is associated with insulin resistance state. Porphyrins can thus regulate the endocrine and reproductive system. The heme deficiency results in dysfunction of nitric oxide synthase, heme oxygenase and cysthathione 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. Heme is also involved in the stress response. Heme deficiency leads to metabolic syndrome x, coronary artery disease and cerebrovascular disease. Mitochondrial dysfunction due to heme deficiency is related to metabolic syndrome x. Deficiency of glutathione system can contribute to free radical injury crucial in metabolic syndrome x, coronary artery disease and cerebrovascular disease. Deficiency of gasotransmitters can contribute to vasospasm important in metabolic syndrome x, coronary artery disease and cerebrovascular disease. Bile acid deficiency can also contribute to metabolic syndrome x, coronary artery disease and cerebrovascular disease. Bile acids bind to FXR receptor regulating glucose and lipid metabolism.[3-5]

The porphyrins can undergo photo-oxidation and autooxidation generating free radicals. The archaeal porphyrins can produce free radical injury. 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. Porphyrins have been related to metabolic syndrome x, coronary artery disease and cerebrovascular disease. The porphyrins can complex and intercalate with the cell membrane producing sodium potassium ATPase inhibition adding on to digoxin mediated inhibition. 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. The porphyrin especially protoporphyrins can bind to peripheral benzodiazepine receptors in the mitochondria and modulate its function, mitochondrial cholesterol transport and steroidogenesis. Peripheral benzodiazepine receptor modulation by protoporphyrins can regulate cell death, cell proliferation, immunity and neural functions. The peripheral benzodiazepine receptor modulation by porphyrins contributes to metabolic syndrome x. The porphyrin photo-oxidation generates 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. Thus the porphyrins are key regulatory molecules modulating all aspects of cell function.[3-5] This porphyrin mediated regulation of cell organelle function contributes to metabolic syndrome x. 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 increased expression of HERV RNA can result in metabolic syndrome x, coronary artery disease and cerebrovascular disease. Redox stress can contribute to metabolic syndrome x, coronary artery disease and cerebrovascular disease[14,15].

The porphyrin photo-oxidation can generate free radicals which can activate NFKB. This can produce immune activation and cytokine mediated injury. The increase in TNF alpha can modulate insulin receptor contributing to insulin resistance. Immune activation has been described in metabolic syndrome x, coronary artery disease and cerebrovascular disease. 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 cross linking 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 pathology implicated in immune activation in metabolic syndrome x, coronary artery disease and cerebrovascular disease[3,4]. 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] The porphyrin photo-oxidation

can generate free radicals inducing HIF alpha. HIF alpha activation contributes to the Warburg phenotype important in metabolic syndrome x, coronary artery disease and cerebrovascular disease[3,4]. The porphyrins can intercalate with DNA producing HERV expression. HERV expression has been related to metabolic syndrome x, coronary artery disease and cerebrovascular disease. 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 the pathogenesis of metabolic syndrome x, coronary artery disease and cerebrovascular disease. This includes CMV, herpes, EBV and H. pylori. Thus the archaeal porphyrins can contribute to the pathogenesis of metabolic syndrome x, coronary artery disease and cerebrovascular disease. Archaeal 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[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. Right hemispheric chemical dominance can contribute to metabolic syndrome x, coronary artery disease and cerebrovascular disease. Altered porphyrin metabolism has been described in metabolic syndrome x, coronary artery disease and cerebrovascular disease. Protoporphyrins block acetyl choline transmission producing a vagal neuropathy with sympathetic overactivity. Vagal neuropathy results in immune activation, vasospasm and vascular disease. A vagal neuropathy underlines metabolic syndrome x. Porphyrin induced increased NMDA transmission and free radical injury can contribute to neuronal degeneration. 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. Altered porphyrin metabolism has been described in Alzheimer's disease and mood disorders which is increased in metabolic syndrome x. 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. The induction of porphyrin synthesis by low level EMF environmental exposure can contribute to the genesis of metabolic syndrome x, coronary artery disease and cerebrovascular disease. Metabolic syndrome x has risen to epidemic proportions due to environmental low level of EMF pollution.

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. The incidence of metabolic syndrome x, coronary artery disease and cerebrovascular disease is high in Scythian races. The majority of our patients belonged to this group[3,4].

Porphyrins thus serve as the principal critical molecules regulating the metabolic pathways and endocrine system. Porphyrin metabolic defects are the basic molecular pathology underlying metabolic syndrome x, coronary artery disease and cerebrovascular disease.

REFERENCES

[1] Eckburg P.B., Lepp, P.W., & Relman, D.A. (2003). Archaea and Their Potential Role in Human Disease. *Infect Immun, 71*, 591-596.

[2] Smit, A., & Mushegian, A. (2000). Biosynthesis of Isoprenoids via Mevalonate in Archaea: The Lost Pathway. *Genome Res, 10*(10), 1468-84.

[3] Puy, H., Gouya, L., & Deybach, J.C. (2010). Porphyrias. *The Lancet*, *375*(9718), 924-937.

[4] Kadish, K.M., Smith, K.M., & Guilard, C. (1999). *Porphyrin Hand Book*. Academic Press, New York: Elsevier.

[5] Gavish, M., Bachman, I., Shoukrun, R., Katz, Y., Veenman, L., Weisinger, G., & Weizman, A. (1999). Enigma of the Peripheral Benzodiazepine Receptor. *Pharmacological Reviews, 51*(4), 629-650.

[6] Richmond, W. (1973). Preparation and Properties of a Cholesterol Oxidase from Nocardia Species and Its Application to the Enzymatic Assay of Total Cholesterol in Serum. *Clin Chem, 19*, 1350-1356.

[7] Snell, E.D., & Snell, C.T. (1961). *Colorimetric Methods of Analysis* (Vol. 3A). New York: Van NoStrand.

[8] Glick, D. (1971). *Methods of Biochemical Analysis* (Vol. 5). New York: Interscience Publishers.

[9] Colowick, Kaplan, N.O. (1955). *Methods in Enzymology* (Vol. 2). New York: Academic Press.

[10] Van der Geize R., Yam, K., Heuser, T., Wilbrink, M.H., Hara, H., & Anderton, M.C. (2007). A Gene Cluster Encoding Cholesterol Catabolism in a Soil Actinomycete Provides Insight into Mycobacterium Tuberculosis Survival in Macrophages. *Proc Natl Acad Sci USA, 104*(6), 1947-52.

[11] Francis, A.J. (1998). Biotransformation of Uranium and Other Actinides in Radioactive Wastes. *Journal of Alloys and Compounds, 271*(273), 78-84.

[12] Schoner, W. (2002). Endogenous Cardiac Glycosides, a New Class of Steroid Hormones. *Eur. J. Biochem, 269*, 2440-2448.

[13] Vainshtein, M., Suzina, N., Kudryashova, E., & Ariskina, E. (2002). New Magnet-Sensitive Structures in Bacterial and Archaeal Cells. *Biol Cell, 94*(1), 29-35.

[14] Tsagris E.M., de Alba, A.E., Gozmanova, M., & Kalantidis, K. (2008). Viroids, *Cell Microbiol, 10*, 2168.

[15] Horie, M., Honda, T., Suzuki, Y., Kobayashi, Y., Daito, T., & Oshida, T. (2010). Endogenous Non-Retroviral RNA Virus Elements in Mammalian Genomes, *Nature, 463*, 84-87.

[16] Kurup, R., & Kurup, P.A. (2009). *Hypothalamic Digoxin, Cerebral Dominance and Brain Function in Health and Diseases*. New York: Nova Science Publishers.

