Chapter 9

The Porphyrions and Genetic Regulation - a Porphyrions Induce Trisomy 21 and Huntington's Disease

Introduction

Actinidic archaea have been related to the pathogenesis of Trisomy 21 and Huntington's disease.[1-5] An actinide dependent shadow biosphere of archaea and viroids in Trisomy 21 and Huntington's disease is described. Actinidic archaea have a mevalonate pathway and are cholesterol catabolizing. They can use cholesterol as a carbon and energy source. Archaeal cholesterol catabolism can generate porphyrins via the cholesterol ring oxidase generated pyruvate and GABA shunt pathway. Porphyrins have been related to Trisomy 21 and Huntington's disease. They can function as self replicating supramolecular organisms which can be called as porphyrions. The role of archaeal porphyrins in regulation of genomic function is discussed.[1-5]

Materials and Methods

The following groups were included in the study: - Trisomy 21 and Huntington's 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. 10 normal people each with right hemispheric, left hemispheric and bi-hemispheric dominance were also 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. 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. Plasma from fasting heparinised blood was used and the experimental protocol was as follows (I) Plasma±phosphate buffered saline, (II) same as I±cholesterol substrate, (III) same as II±rutile 0.1 mg/ml, (IV) same as II±ciprofloxacine and doxycycline each in a concentration of 1 mg/ml. Cholesterol substrate was prepared as described by Richmond. Aliquots were withdrawn at zero time immediately after mixing and after incubation at 37 ℃ for 1 hour. The following estimations were carried out: - Cytochrome F420, free RNA, free DNA, polycyclic aromatic hydrocarbon, hydrogen peroxide, pyruvate, ammonia, glutamate, delta aminolevulinic acid, succinate, glycine and digoxin. Cytochrome F420 was estimated flourimetrically (excitation wavelength 420 nm and emission wavelength 520 nm). Polycyclic aromatic hydrocarbon was estimated by measuring hydrogen peroxide liberated by using glucose reagent. The study also involved estimating the following parameters in the patient population- digoxin, bile acid, hexokinase, porphyrins, pyruvate, glutamate, ammonia, acetyl CoA, acetyl choline, HMG CoA reductase, cytochrome C, blood ATP, ATP synthase, ERV RNA (endogenous retroviral RNA), H_2O_2 (hydrogen peroxide), NOX (NADPH oxidase), TNF alpha and heme oxygenase.[6-9] Informed consent of the subjects and the approval of the ethics committee were obtained for the study. The statistical analysis was done by ANOVA.

Results

Plasma of control subjects showed increased levels of the above mentioned parameters with after incubation for 1 hour and addition of cholesterol substrate resulted in still further significant increase in these parameters. The plasma of patients showed similar results but the extent of increase was more. The addition of antibiotics to the control plasma caused a decrease in all the parameters while addition of rutile increased their levels. The addition of

antibiotics to the patient's plasma caused a decrease in all the parameters while addition of rutile increased their levels but the extent of change was more in patient's sera as compared to controls. The results are expressed in tables section 1: 1-6 as percentage change in the parameters after 1 hour incubation as compared to the values at zero time. There was upregulated archaeal porphyrin synthesis in the patient population which was archaeal in origin as indicated by actinide catalysis of the reactions. The cholesterol oxidase pathway generated pyruvate which entered the GABA shunt pathway. This resulted in synthesis of succinate and glycine which are substrates for ALA synthase.

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

Section 1: Experimental Study

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

Group	CYT F420 % (Increase with Rutile)		CYT F420 % (Decrease with Doxy ±Cipro)		PAH % change (Increase with Rutile)		PAH % change (Decrease with Doxy ±Cipro)	
	Mean	± SD	Mean	± SD	Mean	± SD	Mean	± SD
Normal	4.48	0.15	18.24	0.66	4.45	0.14	18.25	0.72
Trisomy 21	22.12	1.81	61.33	9.82	22.83	1.78	59.84	7.62
HD	22.59	1.86	57.05	8.45	23.40	1.55	65.77	5.27
F value	306.749		130.054		391.318		257.996	
P value	< 0.001		< 0.001		< 0.001		< 0.001	

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

Group	DNA % change (Increase with Rutile)		DNA % change (Decrease with Doxy ±Cipro)		RNA % change (Increase with Rutile)		RNA % change (Decrease with Doxy ±Cipro)	
	Mean	± SD	Mean	± SD	Mean	± SD	Mean	± SD
Normal	4.37	0.15	18.39	0.38	4.37	0.13	18.38	0.48
Trisomy 21	22.62	1.38	63.82	5.53	23.29	1.98	67.46	3.96
HD	23.01	1.67	65.35	3.56	23.33	1.86	66.46	3.65
F value	337.577		356.621		427.828		654.453	
P value	< 0.001		< 0.001		< 0.001		< 0.001	

Table 3. *Effect of rutile and antibiotics on digoxin and delta aminolevulinic acid.*

Group	Digoxin (ng/ml) (Increase with Rutile)		Digoxin (ng/ml) (Decrease with Doxy ±Cipro)		ALA % (Increase with Rutile)		ALA % (Decrease with Doxy ±Cipro)	
	Mean	± SD	Mean	± SD	Mean	± SD	Mean	± SD
Normal	0.11	0.00	0.054	0.003	4.40	0.10	18.48	0.39
Trisomy 21	0.52	0.03	0.214	0.032	22.38	1.79	67.10	3.82
HD	0.47	0.04	0.202	0.025	22.87	1.84	66.31	3.68
F value	135.116		71.706		372.716		556.411	
P value	< 0.001		< 0.001		< 0.001		< 0.001	

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

Group	Succinate % (Increase with Rutile)		Succinate % (Decrease with Doxy ±Cipro)		Glycine % change (Increase with Rutile)		Glycine % change (Decrease with Doxy ±Cipro)	
	Mean	± SD	Mean	± SD	Mean	± SD	Mean	± SD
Normal	4.41	0.15	18.63	0.12	4.34	0.15	18.24	0.37
Trisomy 21	24.10	1.61	65.78	4.43	22.73	2.46	65.87	4.35
HD	23.70	1.75	68.06	3.52	23.81	1.49	64.89	6.01
F value	403.394		680.284		348.867		364.999	
P value	< 0.001		< 0.001		< 0.001		< 0.001	

Table 5. *Effect of rutile and antibiotics on pyruvate and glutamate.*

Group	Pyruvate % change (Increase with Rutile)		Pyruvate % change (Decrease with Doxy ±Cipro)		Glutamate (Increase with Rutile)		Glutamate (Decrease with Doxy ±Cipro)	
	Mean	± SD	Mean	± SD	Mean	± SD	Mean	± SD
Normal	4.34	0.21	18.43	0.82	4.21	0.16	18.56	0.76
Trisomy 21	21.59	1.23	60.28	9.22	22.81	1.91	63.47	5.81
HD	20.67	1.38	58.75	8.12	23.23	1.88	65.11	5.14
F value	321.255		115.242		292.065		317.966	
P value	< 0.001		< 0.001		< 0.001		< 0.001	

Table 6. *Effect of rutile and antibiotics on hydrogen peroxide and ammonia.*

Group	H_2O_2 % (Increase with Rutile)		H_2O_2 % (Decrease with Doxy ±Cipro)		Ammonia % (Increase with Rutile)		Ammonia % (Decrease with Doxy ±Cipro)	
	Mean	± SD	Mean	± SD	Mean	± SD	Mean	± SD
Normal	4.43	0.19	18.13	0.63	4.40	0.10	18.48	0.39
Trisomy 21	21.14	1.20	60.53	4.70	22.38	1.79	67.10	3.82
HD	23.27	1.53	58.91	6.09	22.87	1.84	66.31	3.68
F value	380.721		171.228		372.716		556.411	
P value	< 0.001		< 0.001		< 0.001		< 0.001	

Section 2: Patient Study

Table 1.

Group	RBC Digoxin (ng/ml RBC Susp)		Cytochrome F 420		HERV RNA (ug/ml)		H_2O_2 (umol/ml RBC)	
	Mean	± SD	Mean	± SD	Mean	± SD	Mean	± SD
NO/BHCD	0.58	0.07	1.00	0.00	17.75	0.72	177.43	6.71
RHCD	1.41	0.23	4.00	0.00	55.17	5.85	278.29	7.74
LHCD	0.18	0.05	0.00	0.00	8.70	0.90	111.63	5.40
HD	1.34	0.31	4.00	0.00	51.16	7.78	295.37	3.78
Trisomy 21	1.34	0.25	4.00	0.00	47.28	3.55	283.04	9.17
F value	60.288		0.001		194.418		713.569	
P value	< 0.001		< 0.001		< 0.001		< 0.001	

Table 2.

Group	NOX (OD diff/hr/mgpro)		TNF ALP (pg/ml)		ALA (umol24)		PBG (umol24)	
	Mean	± SD	Mean	± SD	Mean	± SD	Mean	± SD
NO/BHCD	0.012	0.001	17.94	0.59	15.44	0.50	20.82	1.19
RHCD	0.036	0.008	78.63	5.08	63.50	6.95	42.20	8.50
LHCD	0.007	0.001	9.29	0.81	3.86	0.26	12.11	1.34
HD	0.035	0.011	82.13	3.97	67.30	5.98	47.25	4.19
Trisomy 21	0.035	0.009	80.30	6.65	64.99	6.72	45.69	4.18
F value	44.896		427.654		295.467		183.296	
P value	< 0.001		< 0.001		< 0.001		< 0.001	

Table 3.

Group	Uroporphyrin (nmol24)		Coproporphyrin (nmol/24)		Protoporphyrin (Ab unit)		Heme (uM)	
	Mean	± SD	Mean	± SD	Mean	± SD	Mean	± SD
NO/BHCD	50.18	3.54	137.94	4.75	10.35	0.38	30.27	0.81
RHCD	250.28	23.43	389.01	54.11	42.46	6.36	12.47	2.82
LHCD	9.51	1.19	64.33	13.09	2.64	0.42	50.55	1.07
HD	286.84	24.18	432.22	50.11	49.36	4.18	11.81	0.80
Trisomy 21	258.33	37.85	421.52	36.57	50.97	7.07	11.81	1.14
F value	160.533		279.759		424.198		1472.05	
P value	< 0.001		< 0.001		< 0.001		< 0.001	

Table 4.

Group	Bilirubin (mg/dl)		Biliverdin (Ab unit)		ATP Synthase (umol/gHb)		SE ATP (umol/dl)	
	Mean	**± SD**	**Mean**	**± SD**	**Mean**	**± SD**	**Mean**	**± SD**
NO/BHCD	0.55	0.02	0.030	0.001	0.36	0.13	0.42	0.11
RHCD	1.70	0.20	0.067	0.011	2.73	0.94	2.24	0.44
LHCD	0.21	0.00	0.017	0.001	0.09	0.01	0.02	0.01
HD	1.83	0.09	0.071	0.014	3.34	0.84	1.27	0.26
Trisomy 21	1.85	0.07	0.071	0.015	3.15	0.73	1.17	0.11
F value	370.517		59.963		54.754		67.588	
P value	< 0.001		< 0.001		< 0.001		< 0.001	

Table 5.

Group	Cyto C (ng/ml)		Lactate (mg/dl)		Pyruvate (umol/l)		RBC Hexokinase (ug glu phos/ hr/mgpro)	
	Mean	**± SD**	**Mean**	**± SD**	**Mean**	**± SD**	**Mean**	**± SD**
NO/BHCD	2.79	0.28	7.38	0.31	40.51	1.42	1.66	0.45
RHCD	12.39	1.23	25.99	8.10	100.51	12.32	5.46	2.83
LHCD	1.21	0.38	2.75	0.41	23.79	2.51	0.68	0.23
HD	12.65	1.06	24.28	1.69	95.44	12.04	9.30	3.98
Trisomy 21	12.79	1.15	23.69	2.19	91.81	4.12	8.68	2.60
F value	445.772		162.945		154.701		18.187	
P value	< 0.001		< 0.001		< 0.001		< 0.001	

Table 6.

Group	ACOA (mg/dl)		ACH (ug/ml)		Glutamate (mg/dl)	
	Mean	**± SD**	**Mean**	**± SD**	**Mean**	**± SD**
NO/BHCD	8.75	0.38	75.11	2.96	0.65	0.03
RHCD	2.51	0.36	38.57	7.03	3.19	0.32
LHCD	16.49	0.89	91.98	2.89	0.16	0.02
HD	1.95	0.06	35.02	5.85	3.14	0.32
Trisomy 21	2.01	0.08	39.34	8.15	3.30	0.48
F value	1871.04		116.901		200.702	
P value	< 0.001		< 0.001		< 0.001	

Table 7.

Group	Se. Ammonia (ug/dl)		HMG Co A (HMG CoA/MEV)		Bile Acid (mg/ml)	
	Mean	**± SD**	**Mean**	**± SD**	**Mean**	**± SD**
NO/BHCD	50.60	1.42	1.70	0.07	79.99	3.36
RHCD	93.43	4.85	1.16	0.10	25.68	7.04
LHCD	23.92	3.38	2.21	0.39	140.40	10.32
HD	94.60	8.52	1.08	0.13	28.93	4.93
Trisomy 21	98.81	15.65	1.09	0.11	21.31	4.49
F value	61.645		159.963		635.306	
P value	< 0.001		< 0.001		< 0.001	

Abbreviations

NO/BHCD: Normal/Bi-hemispheric chemical dominance
RHCD: Right hemispheric chemical dominance
LHCD: Left hemispheric chemical dominance
HD: Huntington's 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]

Porphyrins can contribute to the pathogenesis of Trisomy 21 and Huntington's disease. The porphyrins can undergo photo-oxidation and auto-oxidation 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 trisomy 21 and Huntington's disease. Protoporphyrins are the endogenous ligand of the peripheral benzodiazepine receptor. Protoporphyrins binding to the mitochondrial peripheral benzodiazepine receptor can mediate cell death. Protoporphyrin binds to the peripheral benzodiazepine receptor regulating steroid and digoxin synthesis. Increased porphyrin metabolites can contribute to

hyperdigoxinemia. Digoxin can modulate the neuro-immuno-endocrine system. Digoxin can inhibit sodium potassium ATPase producing intracellular calcium overload and activation of the caspase cascade producing cell death. Hyperdigoxinemia has been related to neuronal degeneration in Trisomy 21 and Huntington's disease. The porphyrins can complex and intercalate with the cell membrane producing sodium potassium ATPase inhibition adding on to digoxin mediated inhibition. This results in increase in intracellular calcium and decrease in intracellular magnesium. Intracellular magnesium depletion results in chromosomal non disjunction as well as proof-reading errors due to DNA polymerase 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. This can produce defective proof-reading function of DNA polymerase leading on to trinucleotide repeats. This contributes to the pathogenesis of Trisomy 21 and Huntington's disease. 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 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] 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 catalyze 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. The viroids can contribute to neuronal degeneration in Trisomy 21 and Huntington's disease by phenomena of RNA interference. Bacterial and viral infections can precipitate porphyria. Thus porphyrins can regulate genomic function. The increased expression of HERV RNA can result in neuronal degenerations in Trisomy 21 and Huntington's disease by RNA interference.[14, 15]

The possibility of Warburg phenotype induced by actinide based primitive organism like archaea with a mevalonate pathway and cholesterol catabolism in Trisomy 21 and Huntington's disease 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 Alzheimer's disease, Parkinson's disease and motor neuron disease. The increase in glycolytic pathway leads to increase in glyceraldehyde-3-phosphate dehydrogenase. The glyceraldehyde-3-phosphate dehydrogenase gets polyadenylated by redox activated PARP. The polyadenylated glyceraldehyde-3-phosphate dehydrogenase gets transported to the cell nucleus producing nuclear mediated cell death. The increase in glycolysis leads to increase in fructose 1, 6 diphosphate which enters the pentose phosphate pathway generating NADPH leading on to NOX activation. NOX activation induces NMDA excitotoxicity and neuronal cell death. NOX activation also leads to free radical injury, mitochondrial PT pore opening and caspase cascade activity. This leads to mitochondria mediated cell death. The lymphocytes depend on glycolysis for its energy needs. The increase in glycolysis activates the immune system leading to cytokine mediated cell death. Thus the generation of the Warburg phenotype can mediate cell death in Trisomy 21 and Huntington's disease.

The role of porphyrins in regulation of cell functions including cell death in Trisomy 21 and Huntington's disease and neuro-immuno-endocrine integration

is discussed. Porphyrins can combine with membranes modulating membrane function. Porphyrins binding to cell membrane can produce sodium potassium ATPase inhibition and intracellular calcium overload. This can activate the caspase cascade producing cell death. Porphyrins can combine with proteins oxidizing their tyrosine, tryptophan, cysteine and histidine residues producing crosslinking and altering protein conformation and function. Porphyrins can modulate protein conformation. Neurodegenerations like Trisomy 21 and Huntington's disease are basically conformational diseases. The proteins with altered conformation resist lysosomal digestion and accumulate in the cell producing cell death. The increased porphyrin binding to proteins can produce alteration in protein conformation contributing to degenerations. This accounts for amyloid deposition in Trisomy 21. Porphyrins can complex with DNA and RNA modulating their function. Porphyrin interpolating with DNA can alter transcription and generate HERV expression. HERV expression has been related to neurodegenerations in Trisomy 21 and Huntington's disease. 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 can lead to neurodegeneration. The glutathione peroxidase is dysfunctional and the glutathione system of free radical scavenging does not function. Free radical injury and dysfunction of the glutathione system is described in neurodegeneration. 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. Bile acids are neuroprotective and deficiency of bile acids can contribute to neurodegeneration. 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. NO, CO and H_2S can

combine with iron residues in cytochrome c oxidase producing mitochondrial hibernation and cytoprotection. The deficiency of NO, CO and H_2S results in loss of this cytoprotection and neurodegeneration. Heme has got cytoprotective, neuroprotective, anti-inflammatory and antiproliferative effects. Heme deficiency can lead to cytokine mediated cell death and contribute to neurodegeneration in Trisomy 21 and Huntington's disease. Heme is also involved in the stress response.[3-5]

The porphyrin photo-oxidation can generate free radicals which can activate NFKB. This can produce immune activation and cytokine mediated injury. The increase in archaeal porphyrins can lead to Trisomy 21 and Huntington's 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 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] An autoimmune pathology has been related to neurodegenerations in Trisomy 21 and Huntington's disease. Autoimmune disease has been described in Trisomy 21.

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.[3, 4] Insulin resistance can contribute to

neuronal cell death in Trisomy 21 and Huntington's disease. The porphyrin photo-oxidation can generate free radicals inducing HIF alpha and producing oncogene activation. Heme deficiency can lead to activation of HIF alpha. HIF alpha can induce the Warburg phenotype. This can lead to oncogenesis. Trisomy 21 is related to increased incidence of malignancies. The Warburg phenotype can itself induce neurodegenerations in Trisomy 21 and Huntington's disease. The protoporphyrins binding to mitochondrial benzodiazepine receptors can regulate cell proliferation.[3, 4]

The archaea and viroids can regulate the nervous system including the NMDA/GABA thalamo-cortico-thalamic 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 thalamo-cortico-thalamic pathway of conscious perception. The dipolar porphyrins, PAH and archaeal magnetite in the setting of digoxin induced sodium potassium ATPase inhibition can produce a pumped phonon system mediated Frohlich model superconducting state inducing quantal perception with nanoarchaeal sensed gravity producing the orchestrated reduction of the quantal possibilities to the macroscopic world. ALA can produce sodium potassium ATPase inhibition resulting in a pumped phonon system mediated quantal state involving dipolar porphyrins. Porphyrin molecules have a wave particle existence and can bridge the dividing line between quantal state and particulate state. Thus the porphyrins can mediate conscious and quantal perception. Porphyrins binding to proteins, nucleic acids and cell membranes can produce biophoton emission. Porphyrins by auto-oxidation can generate biophotons and are involved in quantal perception. Biophotons can mediate quantal perception. Cellular porphyrins

photo-oxidation are involved in sensing of earth magnetic fields and low level biomagnetic fields. Thus prophyrins can mediate extrasensory perception. The porphyrins can modulate hemispheric dominance. There is increased porphyrin synthesis and RHCD and decreased porphyrin synthesis in LHCD. Porphyrin mediated NMDA excitotoxicity can contribute to neurodegenerations. Porphyria can lead to psychiatric disorders and seizures which can coexist with neurodegeneration. Mood disorders and schizophrenia can coexist with Trisomy 21 and Huntington's disease. Right hemispheric chemical dominance is associated with Trisomy 21 and Huntington's disease. Protoporphyrins block acetyl choline transmission producing a vagal neuropathy with sympathetic overactivity. Blockade in cholinergic transmission can lead to Trisomy 21 and Huntington's disease. Vagal neuropathy results in immune activation and cell death in Trisomy 21 and Huntington's disease. A vagal neuropathy related to porphyrin accumulation can lead to neurodegenerations. Porphyrin induced increased NMDA transmission and free radical injury can contribute to neuronal degeneration. Porphyrin autooxidation related ROS generation can produce NMDA excitotoxicity. ALA accumulation can block GABA transmission which is neuroprotective.[3, 4, 16]

The dipolar porphyrins, PAH and archaeal magnetite in the setting of digoxin induced sodium potassium ATPase inhibition can produce a pumped phonon system mediated Frohlich model superconducting state inducing quantal perception with nanoarchaeal sensed gravity producing the orchestrated reduction of the quantal possibilities to the macroscopic world. ALA can produce sodium potassium ATPase inhibition resulting in a pumped phonon system mediated quantal state involving dipolar porphyrins. Porphyrins by autooxidation can generate biophotons and are involved in quantal perception. Biophotons can mediate quantal perception. Cellular porphyrins photo-oxidation are involved in sensing of earth magnetic fields and low level

biomagnetic fields. Porphyrins can thus contribute to quantal perception. Low level electromagnetic fields and light can induce porphyrin synthesis. Low level EMF can produce ferrochelatase inhibition as well as heme oxygenase induction contributing to heme depletion, ALA synthase induction and increased porphyrin synthesis. Light also induces ALA synthase and porphyrin synthesis. The increased porphyrin synthesized can contribute to increased quantal perception and can modulate conscious perception. The porphyrin induced biophotons and quantal fields can modulate the source from which low level EMF and photic fields were generated. Thus the porphyrin generated by extraneous low level EMF and photic fields can interact with the source of low level EMF and photic fields modulating it. Thus porphyrins can serve as a bridge between the human brain and the source of low level EMF and photic fields. This serves as a mode of communication between the human brain and EMF storage devices like internet. The porphyrins can also serve as the source of communication with the environment. Environmental EMF and chemicals produce heme oxygenase induction and heme depletion increasing porphyrin synthesis, quantal perception and two-way communication. Thus induction of porphyrin synthesis can serve as a mechanism of communication between human brain and the environment by extrasensory perception. Increased exposure to low levels of EMF can lead to neurodegeneration in Trisomy 21 and Huntington's disease.

Porphyrins also have evolutionary significance since porphyria is related to Scythian races and contributes to the behavioural and intellectual characteristics of this group of population. Porphyrins can intercalate into DNA and produce HERV expression. HERV RNA can get converted to DNA by reverse transcriptase which can get integrated into DNA by integrase. This tends to increase the length of the non-coding region of the DNA. The increase in non-coding region of the DNA is involved in primate and human evolution. Thus,

increased rates of porphyrin synthesis would correlate with increase in non-coding DNA length. The alteration in the length of the non-coding region of the DNA contributes to the dynamic nature of the genome. Thus genetic and acquired porphyrias can lead to alteration in the non-coding region of the genome. The alteration of the length of the non-coding region of the DNA contributes to the racial and individual differences in populations. An increased length of non-coding region as well as increased porphyrin synthesis leads to increased cognitive and creative neuronal function. Porphyrins are involved in quantal perception and regulation of the thalamo-cortico-thalamic pathway of conscious perception. Thus genetic and acquired porphyrias contribute to higher cognitive and creative capacity of certain races. Porphyrias are common among Eurasian Scythian races who have assumed leadership roles in communities and groups. Porphyrins have contributed to human and primate evolution.[3, 4] The neurodegenerations like Trisomy 21 and Huntington's disease are common in Scythian races and most of the our patient population belong to this group.

An actinide dependent shadow biosphere of archaea and viroids in Trisomy 21 and Huntington's disease is described. The porphyrins can contribute to the pathogenesis of Trisomy 21 and Huntington's disease. The porphyrin synthesis is crucial in the pathogenesis of these disorders. 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] Porphyrins can intercalate in the cell membrane producing sodium potassium ATPase inhibition. This results in increase in intracellular calcium and decrease in intracellular

magnesium. Intracellular magnesium depletion results in chromosomal non-disjunction as well as proof-reading errors due to DNA polymerase dysfunction. Porphyrins can also intercalate in DNA modulating DNA function and structure. This can also contribute to DNA polymerase proof-reading functional abnormalities and chromosomal non-disjunction. This contributes to the pathogenesis of Trisomy 21 and Huntington's disease. Heme deficiency can produce cytochrome C oxidase deficiency and mitochondrial dysfunction contributing to neurodegeneration. Heme deficiency can lead to deficiency of glutathione peroxidase and produce dysfunction of glutathione system of free radicals scavenging leading to cell death. Protoporphyrins can bind to peripheral benzodiazepine receptor producing cell death. Porphyrin autooxidation related free radical injury can activate NFKB inducing cytokine mediated cell death. Porphyrin auto-oxidation related free radical injury can open the mitochondrial PT pore and produce leakage of cyto C activating the caspase cascade. Porphyrins can intercalate into the cell membrane inducing sodium potassium ATPase inhibition and intracellular calcium overload activating the caspase cascade. Protoporphyrins binding to the peripheral benzodiazepine receptor can induce steroidal endogenous digoxin synthesis producing digoxin mediated cell death. Thus porphyrins are key molecules inducing cell death and the porphyrin metabolic pathway dysfunction is the key molecular abnormality underlying neurodegeneration in Trisomy 21 and Huntington's disease. The porphyrins play a role in genetic regulation and cell division. Porphyrins can intercalate with DNA and RNA modulating their structure and function.

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