Chapter 5

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Endosymbiotic Actinidic Archaeal Cholesterol Catabolic Syndrome – Hypocholesterolemia and Ontogeny of Schizophrenia, Autism and Epilepsy

Introduction

Actinidic archaea have been implicated in the pathogenesis of schizophrenia, autism and epilepsy[1-9]. Actinide based primitive organism like archaea have a mevalonate pathway and cholesterol catabolism. Cholesterol catabolism by actinidic archaea can lead to cholesterol depletion and a hypocholesterolemic state contributing to the pathogenesis of these disorders[10-17].

Archaea can use cholesterol as a carbon and energy source. Archaeal cholesterol catabolism can lead to schizophrenia, autism and epilepsy. Low cholesterol values in populations have been related to high mortality. The archaeal cholesterol catabolizing enzymes were studied and the results in presented in this paper. This can be described as the endosymbiotic actinidic archaeal cholesterol catabolic syndrome[10-17].

Materials and Methods

The following groups were included in the study: – schizophrenia, autism and epilepsy. There were 10 patients in each group and each patient had an age and sex matched healthy control selected randomly from the general population. The blood samples were drawn in the fasting state before treatment was initiated. Plasma from fasting heparinised blood was used and the experimental protocol was as follows (I) Plasma+phosphate buffered saline, (II) same as I+cholesterol substrate, (III) same as II+rutile 0.1 mg/ml, (IV) same as II+ciprofloxacine and doxycycline each in a concentration of 1 mg/ml. Cholesterol substrate was prepared as described by Richmond[18]. Aliquots were withdrawn at zero time immediately after mixing and after incubation at 37^{o}C for 1 hour.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, polycyclic aromatic hydrocarbon, digoxin, bile acid, cholesterol oxidase activity measured by hydrogen peroxide liberation, pyruvate, butyrate and propionate were estimated[19-21]. Cytochrome F420 was estimated flourimetrically (excitation wavelength 420 nm and emission wavelength 520 nm). Polycyclic aromatic hydrocarbon was estimated by measuring hydrogen peroxide liberated by using glucose reagent. Informed consent of the subjects and the approval of the ethics committee were obtained for the study. The statistical analysis was done by ANOVA.

Results

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 1-4 as percentage change in the parameters after 1 hour incubation as compared to the values at zero time.

Table 1 *Effect of rutile and antibiotics on cytochrome F420 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
Schizo	23.24	2.01	58.72	7.08	23.01	1.69	59.49	4.30
Seizure	23.46	1.87	59.27	8.86	22.67	2.29	57.69	5.29
Autism	21.68	1.90	57.93	9.64	22.61	1.42	64.48	6.90
	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 butyrate and propionate generation from cholesterol.*

Group	Butyrate % change (Increase with Rutile)		Butyrate % change (Decrease with Doxy+Cipro)		Propionate % change (Increase with Rutile)		Propionate % change (Decrease with Doxy+Cipro)	
	Mean	± SD	Mean	± SD	Mean	± SD	Mean	± SD
Normal	4.43	0.19	18.13	0.63	4.40	0.10	18.48	0.39
Schizo	22.50	1.66	60.21	7.42	22.52	1.90	66.39	4.20
Seizure	23.81	1.19	61.08	7.38	22.83	1.90	67.23	3.45
Autism	23.52	1.49	63.24	7.36	23.20	1.57	66.65	4.26
	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	

Table 3 *Effect of rutile and antibiotics on digoxin and bile acids.*

Group	Digoxin (ng/ml) (Increase with Rutile)		Digoxin (ng/ml) (Decrease with Doxy+Cipro)		Bile Acids % change (Increase with Rutile)		Bile Acids % change (Decrease with Doxy+Cipro)	
	Mean	± SD	Mean	± SD	Mean	± SD	Mean	± SD
Normal	0.11	0.00	0.054	0.003	4.29	0.18	18.15	0.58
Schizo	0.55	0.06	0.219	0.043	23.20	1.87	57.04	4.27
Seizure	0.51	0.05	0.199	0.027	22.61	2.22	66.62	4.99
Autism	0.53	0.08	0.205	0.041	22.21	2.04	63.84	6.16
	F value 135.116 P value < 0.001		F value 71.706 P value < 0.001		F value 290.441 P value < 0.001		F value 203.651 P value < 0.001	

Table 4 *Effect of rutile and antibiotics on pyruvate and hydrogen peroxide.*

Group	Pyruvate % change (Increase with Rutile)		Pyruvate % change (Decrease with Doxy+Cipro)		H_2O_2 % (Increase with Rutile)		H_2O_2 % (Decrease with Doxy+Cipro)	
	Mean	**± SD**	**Mean**	**± SD**	**Mean**	**± SD**	**Mean**	**± SD**
Normal	4.34	0.21	18.43	0.82	4.43	0.19	18.13	0.63
Schizo	20.99	1.46	61.23	9.73	22.50	1.66	60.21	7.42
Seizure	20.94	1.54	62.76	8.52	23.81	1.19	61.08	7.38
Autism	21.91	1.71	58.45	6.66	23.52	1.49	63.24	7.36
	F value 321.255 P value < 0.001		F value 115.242 P value < 0.001		F value 380.721 P value < 0.001		F value 171.228 P value < 0.001	

Discussion

There was increase in cytochrome F420 indicating archaeal growth. The archaea can synthesise and use cholesterol as a carbon and energy source[22-24]. 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[22-24]. The archaeal beta hydroxyl steroid dehydrogenase activity indicating digoxin synthesis and archaeal cholesterol hydroxylase activity indicating bile acid synthesis were increased[22-24]. The archaeal cholesterol oxidase activity was increased resulting in generation of pyruvate and hydrogen peroxide[22-24]. The pyruvate gets converted to glutamate and ammonia by the GABA shunt pathway. The archaeal aromatization of cholesterol generating PAH was also detected[22-24]. This indicates archaeal cholesterol aromatase activity. The archaeal cholesterol side chain oxidase activity generates butyrate and propionate. Thus archaeal cholesterol oxidase, cholesterol aromatase, cholesterol side chain oxidase, cholesterol hydroxylase and beta hydroxyl steroid dehydrogenase activity were detected in high levels in the patient population of schizophrenia, autism and epilepsy. The archaeal cholesterol catabolising enzymes

were actinide dependent. The archaea can undergo magnetite and calcium carbonate mineralization and can exist as calcified nanoforms[25]. This leads to a cholesterol depleted state and hypocholesterolemic syndrome in patients with schizophrenia, autism and epilepsy.

Low cholesterol has been related to schizophrenia, autism and epilepsy. Low cholesterol is detected in patients with schizophrenia, autism and epilepsy. Cholesterol is required for the formation of synaptic connectivity in neuronal cultures. Depletion of cholesterol from the brain results in loss of synaptic connectivity in multiple neuronal circuits contributing to neuropsychiatric disorders. Cholesterol is required for contact inhibition. Absence of cholesterol results in loss of contact inhibition and uncontrolled and disordered cell proliferation. Low cholesterol has been related to immune activation crucial in schizophrenia, autism and epilepsy[10-17].

The gut endotoxins and lipopolysaccharides are absorbed along with fat producing the syndrome of metabolic endotoxaemia. The endotoxins and lipopolysaccharides can combine with lipoproteins and are detoxified. Metabolic endotoxaemia produces chronic immune activation and generation of superantigens. This has been related to the genesis of autoimmunity important in schizophrenia, autism and epilepsy. Metabolic endotoxaemia results in immune activation and generation of TNF alpha which modulates the insulin receptor producing insulin resistance. Insulin resistance is related to schizophrenia, autism and epilepsy. Metabolic endotoxaemia has been related to schizophrenia, autism and epilepsy. Metabolic endotoxaemia related chronic immune activation drives the retroviral state. Human endogenous retroviruses have been related to schizophrenia, autism and epilepsy. Metabolic endotoxaemia can induce NFKB which can drive oncogene activation crucial in schizophrenia, autism and epilepsy. Thus hypocholesterolemia leads to non-detoxification of endotoxins

and lipopolysaccharides resulting in schizophrenia, autism and epilepsy[10-17].

Infections have been related to schizophrenia, autism and epilepsy. Toxoplasmosis has been related to schizophrenia. Gut bacteria with increase in gut firmicutes and decrease in bacteroides have been related to insulin resistance important in schizophrenia, autism and epilepsy. Chlamydial infections have been related to schizophrenia, autism and epilepsy. Low cholesterol leads to lack of lipoprotein binding to endotoxins[10-17]. The endotoxins and lipopolysaccharides are not detoxified.

Viral diseases have been related to the pathogenesis of schizophrenia, autism and epilepsy. The virus binds to lipid microdomains in the cell membrane. Cholesterol depletion leads to alteration in lipid microdomains and increased entry of virus in the cell. Herpes virus infection and borna virus disease leads to schizophrenia. Retroviral infection-exogenous and endogenous have been related to schizophrenia, autism and epilepsy. Prion disease has been related to alterations in cholesterol metabolism. Prion protein is related to the origin of schizophrenia, autism and epilepsy. Thus a cholesterol depleted state can lead to increased predilection to viral infection and schizophrenia, autism and epilepsy[10-17].

The actinidic archaea uses cholesterol catabolism to generate energy. The cholesterol catabolizing enzymes of the archaea are dependent on actinides. The archaeal cholesterol catabolism leads to a cholesterol depleted state and schizophrenia, autism and epilepsy. Cholesterol depleted state have been related to high mortality. This can be described as the endosymbiotic actinidic archaeal cholesterol catabolic syndrome[10-17].

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