



Chapter 8

Endosymbiotic Actinidic Archaeal Mediated Warburg Phenotype Mediates the Ontogenesis of Schizophrenia, Autism and Epilepsy -

Introduction

Dietary fibre deficiency leads to increased endosymbiotic as well as colonic archaeal growth. Endomyocardial fibrosis along with the root wilt disease of coconut is endemic to Kerala with its radioactive actinide beach sands. Actinides like rutile as well as organisms like phytoplasmas and viroids have been implicated in the etiology of these diseases.¹⁻⁴ The Warburg phenotype has been related to the pathogenesis of schizophrenia, autism and epilepsy.⁴ The possibility of Warburg phenotype induced by actinide based primitive organism like archaea with a mevalonate pathway and cholesterol catabolism was considered in this paper.⁵⁻⁸ An actinide dependent shadow biosphere of archaea and viroids in schizophrenia, autism and epilepsy is described.^{7,9}

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 and, (IV) same as II+ciprofloxacin and doxycycline each in a concentration of 1 mg/ml. Cholesterol substrate was prepared as described by Richmond.¹⁰ Aliquots were withdrawn at zero time immediately after mixing and after incubation at 37 °C for 1 hour. The following estimations were carried out: - Cytochrome F420 and hexokinase.¹¹⁻¹³ Cytochrome F420 was estimated fluorimetrically (excitation wavelength 420 nm and emission wavelength 520 nm). Informed consent of the subjects and the

approval of the ethics committee were obtained for the study. The statistical analysis was done by ANOVA.

Results

Plasma of control subjects showed increased levels of the above mentioned parameters with after incubation for 1 hour and addition of cholesterol substrate resulted in still further significant increase in these parameters. The plasma of patients showed similar results but the extent of increase was more. The addition of antibiotics to the control plasma caused a decrease in all the parameters while addition of rutile increased their levels. The addition of antibiotics to the patient's plasma caused a decrease in all the parameters while addition of rutile increased their levels but the extent of change was more in patient's sera as compared to controls. The results are expressed in tables 1-2 as percentage change in the parameters after 1 hour incubation as compared to the values at zero time.

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

Group	CYT F420 % (Increase with Rutile)		CYT F420 % (Decrease with Doxy+Cipro)	
	Mean	±SD	Mean	±SD
Normal	4.48	0.15	18.24	0.66
Schizo	23.24	2.01	58.72	7.08
Seizure	23.46	1.87	59.27	8.86
Autism	21.68	1.90	57.93	9.64
F value	306.749		130.054	
P value	< 0.001		< 0.001	

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

Group	Hexokinase % change (Increase with Rutile)		Hexokinase % change (Decrease with Doxy+Cipro)	
	Mean	±SD	Mean	±SD
Normal	4.21	0.16	18.56	0.76
Schizo	23.01	2.61	65.87	5.27
Seizure	23.33	1.79	62.50	5.56
Autism	22.88	1.87	65.45	5.08
F value	292.065		317.966	
P value	< 0.001		< 0.001	

Discussion

Dietary Fibre Deficiency, Endosymbiotic Archaea, Cholesterol Catabolism and Neuropsychiatric Disease

Dietary fibre deficiency leads to increased endosymbiotic as well as colonic archaeal growth. There was increase in cytochrome F420 indicating archaeal growth. The archaea can synthesise and use cholesterol as a carbon and energy source.^{6, 14} The archaeal origin of the enzyme activities was indicated by antibiotic induced suppression. The study indicates the presence of actinide based archaea with an alternate actinide based enzymes or metalloenzymes in the system as indicated by rutile induced increase in enzyme activities.^{15, 16} The archaeal glycolytic hexokinase activity were increased. The part of the increased glycolytic hexokinase activity detected is human. The archaea can undergo magnetite and calcium carbonate mineralization and can exist as calcified nanoforms.¹⁷

Dietary Fibre Deficiency, Endosymbiotic Archaea, Warburg Phenotype and Neuropsychiatric Disease

Archaea can induce the host AKT PI3K, AMPK, HIF alpha and NFkB producing the Warburg metabolic phenotype.¹⁸ The increased glycolytic

hexokinase activity indicates the generation of the Warburg phenotype. The generation of the Warburg phenotype is due to activation of HIF alpha. This stimulates anaerobic glycolysis, inhibits pyruvate dehydrogenase, inhibits mitochondrial oxidative phosphorylation, stimulates heme oxygenase, stimulates VEGF and activates nitric oxide synthase. This can lead to increased cell proliferation and oncogene activation. Oncogene activation can occur in schizophrenia, autism and epilepsy. The mitochondrial PT pore hexokinase is increased leading onto cell proliferation. There is induction of glycolysis, inhibition of PDH activity and mitochondrial dysfunction resulting in inefficient energetics and insulin resistance. The archaea and viroid generated cytokines can lead to TNF alpha induced insulin resistance and schizophrenia, autism and epilepsy. The increase in glycolysis can activate glyceraldehyde 3-phosphate dehydrogenase which gets translocated to the nucleus after polyadenylation. The PARP enzyme is activated by glycolysis mediated redox stress. This can produce nuclear cell death and neuronal degeneration in brain areas producing schizophrenia, autism and epilepsy. The increase in the glycolytic enzyme fructose 1,6-diphosphatase increases the pentose phosphate pathway. This generates NADPH which activates NOX. NOX activation is related to NMDA activation and glutamate excitotoxicity. This leads onto schizophrenia, autism and epilepsy.¹⁸

Dietary Fibre Deficiency, Endosymbiotic Archaea, Warburg Phenotype, Free Radical Generation and Neuropsychiatric Disease

The increase in glycolysis activates the enzyme fructose 1,6-diphosphatase which activates the pentose phosphate pathway liberating NADPH. This increases NOX activity generating free radical stress and H₂O₂. Free radical stress is related to insulin resistance. Insulin resistance is related to schizophrenia, autism and epilepsy. Free radicals can activate NFkB producing immune activation and autoimmunity. Autoimmunity is related to schizophrenia,

autism and epilepsy. Free radicals can open the mitochondrial PT pore, produce release of cyto C and activate the caspase cascade. This produces mitochondrial dysfunction resulting in schizophrenia, autism and epilepsy. The free radicals can activate NMDA receptor and induce the enzyme GAD generating GABA. This activates the NMDA/GABA thalamo-cortico-thalamic pathway mediating conscious perception. Increased free radical generation can also initiate schizophrenia. Free radicals can also produce oncogene activation producing schizophrenia, autism and epilepsy. Free radicals can produce HDAC inhibition and HERV generation. The encapsulation of HERV particles in phospholipids vesicles can mediate the generation of schizophrenia, autism and epilepsy.¹⁸

Dietary Fibre Deficiency, Endosymbiotic Archaea, Warburg Phenotype, Immune Activation and Neuropsychiatric Disease

The lymphocytes depend on glycolysis for its energy needs. The increase in glycolysis owing to the induction of Warburg phenotype can lead to immune activation. Immune activation can lead to autoimmunity. Autoimmunity is important in schizophrenia, autism and epilepsy. TNF alpha can activate the NMDA receptor leading to glutamate excitotoxicity. TNF alpha activating NMDA receptor can contribute to schizophrenia. TNF alpha can induce expression of HERV particles contributing to genesis of schizophrenia, autism and epilepsy. TNF alpha can also act upon the insulin receptor producing insulin resistance. NOX activation consequent to the generation of the Warburg phenotype also activates the insulin receptor. Thus there is a hyperinsulinemic state leading on to schizophrenia, autism and epilepsy.¹⁸

Dietary Fibre Deficiency, Endosymbiotic Archaea and Warburg Phenotype - The Basis of Neuropsychiatric Disease

Thus the induction of the Warburg phenotype can lead to schizophrenia, autism and epilepsy. The Warburg phenotype leads to inhibition of pyruvate

dehydrogenase and accumulation of pyruvate. The accumulated pyruvate enters the GABA shunt pathway and is converted to citrate which is acted upon by citrate lyase and converted to acetyl CoA, used for cholesterol synthesis. The pyruvate can be converted to glutamate and ammonia which is oxidised by archaea for energy needs. The increased cholesterol substrate leads to increased archaeal growth and further induction of the Warburg phenotype.¹⁸

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