

# **Chapter 11**

**Endosymbiotic Actinidic Archaeal Mediated  
Warburg Phenotype Mediates Pathogenesis  
of Neurodegeneration - Alzheimer's Disease,  
Parkinson's Disease and  
Motor Neuron Disease**

## Introduction

There is dietary fibre deficiency and increased endosymbiotic as well as colonic archaeal growth in neurodegeneration. Actinides like rutile as well as organisms like phytoplasmas and viroids have been implicated in the etiology of neurodegeneration-Alzheimer's disease, Parkinson's disease and motor neuron disease.<sup>1-4</sup> The Warburg phenotype has been related to the pathogenesis of neurodegeneration-Alzheimer's disease, Parkinson's disease and motor neuron disease.<sup>4</sup> 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.<sup>5-8</sup> An actinide dependent shadow biosphere of archaea and viroids in the above mentioned disease states is described.<sup>7,9</sup>

## Materials and Methods

The following groups were included in the study: - neurodegeneration - Alzheimer's disease, Parkinson's disease and motor neuron 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+ciprofloxacin and doxycycline each in a concentration of 1 mg/ml. Cholesterol substrate was prepared as described by Richmond.<sup>10</sup> Aliquots were withdrawn at zero time immediately after mixing and after incubation at 37 °C for 1 hour.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.<sup>11-13</sup> 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
PD	23.46	1.87	59.27	8.86
AD	23.12	2.00	56.90	6.94
MND	22.70	1.87	60.46	8.06
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
PD	23.33	1.79	62.50	5.56
AD	22.96	2.12	65.11	5.91
MND	21.66	1.94	67.03	5.97
F value	292.065		317.966	
P value	< 0.001		< 0.001	

## Discussion

### Dietary Fibre Deficiency, Endosymbiotic Archaea and Warburg Phenotype - Relation to Neurodegeneration

There is dietary fibre deficiency and increased endosymbiotic as well as colonic archaeal growth in neurodegeneration. There was increase in cytochrome F420 indicating archaeal growth. The archaea can synthesize and use cholesterol as a carbon and energy source.<sup>6, 14</sup> 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.<sup>15, 16</sup> 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.<sup>17</sup> This can contribute to the pathogenesis of neurodegeneration-Alzheimer's disease, Parkinson's disease and motor neuron disease.

Archaea can induce the host AKT PI3K, AMPK, HIF alpha and NFKB producing the Warburg metabolic phenotype.<sup>18</sup> 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 neurodegeneration-Alzheimer's disease, Parkinson's disease and motor neuron disease. There is induction of glycolysis, inhibition of PDH activity and mitochondrial dysfunction resulting in inefficient energetics and insulin resistance. Insulin resistance is important in neurodegeneration-Alzheimer's disease, Parkinson's disease and motor neuron disease. The archaea and viroid generated cytokines can lead to TNF alpha induced insulin resistance and neurodegeneration-Alzheimer's disease, Parkinson's disease and motor neuron disease. 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. 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 neuronal degeneration.<sup>18</sup>

### **Dietary Fibre Deficiency, Endosymbiotic Archaea and Warburg Phenotype Mediated Free Radical Stress - Relation to Neurodegeneration**

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 H<sub>2</sub>O<sub>2</sub>. Free radical stress is related to insulin resistance and neurodegeneration-Alzheimer's disease, Parkinson's disease and motor neuron disease. Free radicals can activate NFKB producing immune activation and autoimmunity in neurodegeneration-Alzheimer's disease,

Parkinson's disease and motor neuron disease. Free radicals can open the mitochondrial PT pore, produce release of cyto C and activate the caspase cascade. This produces cell death and neuronal degeneration. The free radicals can activate NMDA receptor. Increased NMDA excitotoxicity can lead to neurodegeneration-Alzheimer's disease, Parkinson's disease and motor neuron disease. Free radicals can produce HDAC inhibition and HERV generation. The encapsulation of HERV particles in phospholipids vesicles can mediate the generation of the acquired immunodeficiency syndrome. HERV particles can contribute to neurodegeneration-Alzheimer's disease, Parkinson's disease and motor neuron disease.<sup>18</sup>

### **Dietary Fibre Deficiency, Endosymbiotic Archaea and Warburg Phenotype Mediated Lymphocyte Activation - Relation to Neurodegeneration**

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 in neurodegeneration-Alzheimer's disease, Parkinson's disease and motor neuron disease. TNF alpha can activate the NMDA receptor leading to glutamate excitotoxicity and neuronal degeneration. TNF alpha activating NMDA receptor can contribute to neurodegeneration-Alzheimer's disease, Parkinson's disease and motor neuron disease. TNF alpha can induce expression of HERV particles contributing to pathogenesis of neurodegeneration-Alzheimer's disease, Parkinson's disease and motor neuron disease. TNF alpha can also act upon the insulin receptor producing insulin resistance important in neurodegeneration-Alzheimer's disease, Parkinson's disease and motor neuron disease. NOX activation consequent to the generation of the Warburg phenotype also activates the insulin receptor. Thus there is a hyperinsulinemic

state leading on to insulin resistance and neurodegeneration-Alzheimer's disease, Parkinson's disease and motor neuron disease.<sup>18</sup>

Thus the induction of the Warburg phenotype can lead to neurodegeneration-Alzheimer's disease, Parkinson's disease and motor neuron disease. 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.<sup>18</sup> The Warburg phenotype is important in the pathogenesis of neurodegeneration-Alzheimer's disease, Parkinson's disease and motor neuron disease.

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