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Endosymbiotic Actinidic Archaea/Viroids, Hemispheric Dominance and the Tridosha Theory

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Abstract

Objective: Endogenous digoxin has been related to hemispheric dominance. Right hemispheric dominant individuals were hyperdigoxinemic, left hemispheric dominant individuals were hypodigoxinemic and bihemispheric dominant individuals were normodigoxinemic. The possibility of endogenous digoxin synthesis by actinide based primitive organism like archaea with a mevalonate pathway and cholesterol catabolism was considered. An actinide dependent shadow biosphere of archaea and viroids in normal humans and disease states is described. The intracellular endosymbionts archaea and their intron derived viroids constitute the third element regulating the human body. Ayurveda, the traditional Indian System of Medicine, deals with the theory of the three tridosha states (both physical and psychological): Vata, Pitta, and Kapha. The Kapha state has been demonstrated as equivalent to right hemispheric dominant hyperdigoxinemic state. The Pitta state has been demonstrated as equivalent to the left hemispheric dominant hypodigoxinemic state. The Vata state has been demonstrated as equivalent to the bihemispheric dominant normodigoxinemic state[8]. The study assessed actinidic archaea and viroids in the tridosha states of Ayurveda. The results are presented in this paper.

Methods: The following groups were included in the study:- (I) right handed-left hemispheric dominant-pitta group, (II) left handed-right hemispheric dominant-kapha group and (III) amphidextrous-bihemispheric dominant-vata group of individuals. Cholesterol substrate was added to the plasma of the patients and the generation of cytochrome F420, free RNA, free DNA, polycyclic aromatic hydrocarbon, hydrogen peroxide, serotonin, pyruvate, ammonia, glutamate, cytochrome C, hexokinase, ATP synthase, HMG CoA reductase, digoxin and bile acids were studied. The changes with the addition of antibiotics and rutile to the patient's plasma were also studied.

Results: The plasma of the bihemispheric dominant vata group showed detectable levels of the above mentioned parameters after incubation for 1 hour and addition of cholesterol substrate resulted in still further increase in these parameters. The addition of antibiotics to the bihemispheric dominant vata group caused a decrease in all the parameters while addition of rutile increased their levels. The plasma of right hemispheric dominant kapha group showed a significant increase in the above mentioned parameters as compared to bihemispheric dominant vata group. The addition of antibiotics to the right hemispheric dominant kapha group caused a decrease in all the parameters while addition of rutile increased their levels but the extent of change was more in right hemispheric dominant kapha group as compared to bihemispheric dominant vata group. The plasma of left hemispheric dominant pitta group showed a significant decrease in the above mentioned parameters as compared to the bihemispheric dominant vata group. The addition of antibiotics to the left hemispheric dominant pitta group caused a decrease in all the parameters while addition of rutile increased their levels but the extent of change was less in left hemispheric dominant pitta group as compared to bihemispheric dominant vata group.

Conclusion: The third element formed of intracellular archaea and viroidal symbiosis determines hemispheric dominance and tridoshas. Also archaeal cholesterol synthesis and cholesterol catabolism determines hemispheric dominance and tridoshas. The archaea and viroidal density is high in right hemispheric dominant kapha group, intermediate in bihemispheric dominant vata group and low in left hemispheric dominant pitta group.

Key words: Archaea; Viroids; Cholesterol; Digoxin; Hemispheric dominance; Tridoshas; Vata; Pitta; Kapha

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INTRODUCTION

The human brain synthesises an endogenous membrane sodium-potassium ATPase inhibitor digoxin which plays a role in neuro-immuno-endocrine integration and pathogenesis of several neuropsychiatric and systemic diseases. Endomyocardial fibrosis (EMF) along with the root wilt disease of coconut is endemic to Kerala with its radioactive actinide beach sands. Actinides like rutile producing intracellular magnesium deficiency due to rutile-magnesium exchange sites in the cell membrane has been implicated in the etiology of EMF[1]. Endogenous digoxin, a steroidal glycoside which functions as a membrane sodium-potassium ATPase inhibitor has also been related to its etiology due to the intracellular magnesium deficiency it produces[2]. Organisms like phytoplasmas and viroids have also been demonstrated to play a role in the etiology of these diseases[3, 4]. Endogenous digoxin has been related to hemispheric dominance[2]. Right hemispheric dominant individuals were hyperdigoxinemic, left hemispheric dominant individuals were hypodigoxinemic and bihemispheric dominant individuals were normodigoxinemic. The possibility of endogenous digoxin synthesis by actinide based primitive organism like archaea with a mevalonate pathway and cholesterol catabolism was considered[5, 6, 7]. An actinide dependent shadow biosphere of archaea and viroids in the above mentioned disease states is described[6]. The intracellular endosymbionts archaea and their intron derived viroids constitute the third element regulating the human body.

Ayurveda, the traditional Indian System of Medicine, deals with the theory of the three tridosha states (both physical and psychological): Vata, Pitta, and Kapha. They are the three major human constitutional types that both depend on psychological and physical characteristics. The Pitta state is described as a critical, discriminative, and rational psychological state of mind, while the Kapha state is described as being dominant for emotional stimuli. The Vata state is an intermediate unstable shifting state. The Pitta types are of average height and built with well developed musculature. The Vata types are thin individuals with low body mass index. The Kapha types are short stocky individuals that tend toward obesity, and who are sedentary. Previous work in our laboratory had correlated the tridosha states of Kapha, Pitta and Vata with hemispheric dominance and endogenous digoxin status. The Kapha state has been demonstrated as equivalent to right hemispheric dominant hyperdigoxinemic state. The Pitta state has been demonstrated as equivalent to the left hemispheric dominant hypodigoxinemic state. The Vata state has been demonstrated as equivalent to the bihemispheric dominant normodigoxinemic state[8]. The study assessed actinidic archaea and viroids in the tridosha states of Ayurveda. The results are presented in this paper.

METHODS

Informed consent of the subjects and the approval of the ethics committee were obtained for the study. The following groups were included in the study:- (I) right handed-left hemispheric dominant-pitta group, (II) left handed-right hemispheric dominant-kapha group and (III) amphidextrous-bihemispheric dominant-vata group of individuals. Hemispheric dominance was assessed by methods described in previous reports[2]. There were 10 healthy normal individuals in the age range between 20 to 30 years in each group. They were selected randomly from the general population. The blood samples were drawn in the fasting state. 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[9]. 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, muramic acid, polycyclic aromatic hydrocarbon, hydrogen peroxide, dopamine, pyruvate, ammonia, glutamate, cytochrome C, hexokinase, ATP synthase, HMG CoA reductase, digoxin and bile acids[10, 11, 12, 13]. 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 statistical analysis was done by ANOVA.

RESULTS

The parameters checked as indicated above were:- cytochrome F420, free RNA, free DNA, muramic acid, polycyclic aromatic hydrocarbon, hydrogen peroxide, serotonin, pyruvate, ammonia, glutamate, cytochrome C, hexokinase, ATP synthase, HMG CoA reductase, digoxin and bile acids. The plasma of the bihemispheric dominant group showed detectable levels of the above mentioned parameters after incubation for 1 hour and addition of

cholesterol substrate resulted in still further increase in these parameters. The addition of antibiotics to the **bihemispheric dominant vata group** caused a decrease in all the parameters while addition of rutile increased their levels. The plasma of **right hemispheric dominant kapha group** showed a significant increase in the above mentioned parameters as compared to **bihemispheric dominant vata group**. The addition of antibiotics to the **right hemispheric dominant kapha group** caused a decrease in all the parameters while addition of rutile increased their levels but the extent of change was more in **right hemispheric dominant kapha group** as compared to **bihemispheric dominant vata group**. The plasma of **left hemispheric dominant pitta group** showed a significant decrease in the above mentioned parameters as compared to the **bihemispheric dominant vata group**. The addition of antibiotics to the **left hemispheric dominant pitta group** caused a decrease in all the parameters while addition of rutile increased their levels but the extent of change was less in **left hemispheric dominant pitta group** as compared to **bihemispheric dominant vata group**. The results are expressed in tables 1-7 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 CYT F420 and Muramic Acid

Group	CYT F420% change (Increase with Rutile)		CYT F420% change (Decrease with antibiotics)		Muramic acid % change (Increase with Rutile)		Muramic acid % change (Decrease with antibiotics)	
	Mean	± SD	Mean	± SD	Mean	± SD	Mean	± SD
BHD/VATA	4.48	0.15	18.24	0.66	4.34	0.15	18.24	0.37
RHD/KAPHA	11.35	0.64	60.49	6.22	22.68	1.99	63.29	5.93
LHD/PITTA	2.13	0.13	5.37	1.47	2.26	0.25	7.45	0.40
F value	306.749		130.054		348.867		364.999	
P value	< 0.001		< 0.001		< 0.001		< 0.001	

Table 2
Effect of Rutile and Antibiotics on Free DNA and RNA

Group	DNA % change (Increase with Rutile)		DNA % change (Decrease with antibiotics)		RNA % change (Increase with Rutile)		RNA % change (Decrease with antibiotics)	
	Mean	± SD	Mean	± SD	Mean	± SD	Mean	± SD
BHD/VATA	4.37	0.15	18.39	0.38	4.37	0.13	18.38	0.48
RHD/KAPHA	22.99	1.56	65.19	4.10	23.27	1.36	65.66	3.93
LHD/PITTA	2.26	0.25	7.45	0.40	2.30	0.12	7.62	0.30
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 HMG CoA Reductase and PAH

Group	HMG CoA R% change (Increase with Rutile)		HMG CoA R% change (Decrease with antibiotics)		PAH % change (Increase with Rutile)		PAH % change (Decrease with antibiotics)	
	Mean	± SD	Mean	± SD	Mean	± SD	Mean	± SD
BHD/VATA	4.30	0.20	18.35	0.35	4.45	0.14	18.25	0.72
RHD/KAPHA	21.06	2.32	63.87	6.22	21.00	2.54	57.42	7.07
LHD/PITTA	2.33	0.17	7.24	0.59	2.25	0.17	7.01	0.65
F value	319.332		199.553		391.318		257.996	
P value	< 0.001		< 0.001		< 0.001		< 0.001	

Table 4
Effect of Rutile and Antibiotics on Digoxin and Bile Acids

Group	Digoxin (ng/ml) (Increase with Rutile)		Digoxin (ng/ml) (Decrease with antibiotics)		Bile Acids% change (Increase with Rutile)		Bile Acids% change (Decrease with antibiotics)	
	Mean	± SD	Mean	± SD	Mean	± SD	Mean	± SD
BHD/VATA	0.11	0.00	0.054	0.003	4.29	0.18	18.15	0.58
RHD/KAPHA	0.55	0.10	0.248	0.058	21.10	2.43	54.82	8.28
LHD/PITTA	0.07	0.01	0.026	0.004	2.25	0.19	7.25	0.66
F value	135.116		71.706		290.441		203.651	
P value	< 0.001		< 0.001		< 0.001		< 0.001	

Table 5
Effect of Rutile and Antibiotics on Pyruvate and Hexokinase

Group	Pyruvate % change (Increase with Rutile)		Pyruvate % change (Decrease with antibiotics)		Hexokinase% change (Increase with Rutile)		Hexokinase % change (Decrease with antibiotics)	
	Mean	± SD	Mean	± SD	Mean	± SD	Mean	± SD
BHD/VATA	4.34	0.21	18.43	0.82	4.21	0.16	18.56	0.76
RHD/KAPHA	11.12	0.66	59.68	6.24	23.27	1.68	67.35	3.77
LHD/PITTA	2.16	0.18	5.91	1.38	2.24	0.17	6.29	1.06
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 ATP Synthase and Hydrogen Peroxide

Group	ATP synthase % change (Increase with Rutile)		ATP synthase % change (Decrease with antibiotics)		H_2O_2 % change (Increase with Rutile)		H_2O_2 % change (Decrease with antibiotics)	
	Mean	± SD	Mean	± SD	Mean	± SD	Mean	± SD
BHD/VATA	4.40	0.11	18.78	0.11	4.43	0.19	18.13	0.63
RHD/KAPHA	11.99	0.38	66.34	3.39	17.60	3.53	54.68	5.09
LHD/PITTA	2.30	0.12	7.62	0.30	2.24	0.23	5.36	0.99
F value	449.503		673.081		380.721		171.228	
P value	< 0.001		< 0.001		< 0.001		< 0.001	

Table 7
Effect of Rutile and Antibiotics on Delta Amino Levulinic Acid and Dopamine

Group	ALA % (Increase with Rutile)		ALA % (Decrease with antibiotics)		DOPAMINE% change (Increase with Rutile)		DOPAMINE% change (Decrease with antibiotics)	
	Mean	± SD	Mean	± SD	Mean	± SD	Mean	± SD
BHD/VATA	4.40	0.10	18.48	0.39	4.41	0.15	18.63	0.12
RHD/KAPHA	22.98	2.06	66.10	4.03	11.36	0.58	65.41	4.83
LHD/PITTA	2.13	0.11	7.62	0.32	2.13	0.11	7.62	0.32
F value	372.716		556.411		403.394		680.284	
P value	< 0.001		< 0.001		< 0.001		< 0.001	

Abbreviation
BHD: Bihemispheric dominance/vata
RHD: Right hemispheric dominance/kapha
LHD: Left hemispheric dominance/pitta

DISCUSSION

Ayurveda, the traditional Indian System of Medicine, deals with the theory of the three tridosha states (both physical and psychological): Vata, Pitta, and Kapha. They are the three major human constitutional types that both depend on psychological and physical characteristics. The Pitta state is described as a critical, discriminative, and rational psychological state of mind, while the Kapha state is described as being dominant for emotional stimuli. The Vata state is an intermediate unstable shifting state. The Pitta types are of average height and built with well developed musculature. The Vata types are thin individuals with low body mass index. The Kapha types are short stocky individuals that tend toward obesity, and who are sedentary. The study assessed the biochemical differences between right hemispheric dominant, bihemispheric dominant, and left hemispheric dominant individuals, and then compared this with the patterns obtained in the Vata, Pitta, and Kapha states. The isoprenoid metabolites (digoxin, dolichol, and ubiquinone), glycoconjugate metabolism, free radical metabolism, and the RBC membrane composition were studied. The hemispheric chemical dominance in various systemic diseases and psychological states was also investigated. The results showed that right hemispheric chemically dominant/ Kapha state had elevated digoxin levels, increased free radical production and reduced scavenging, increased tryptophan catabolites and reduced tyrosine catabolites, increased glycoconjugate levels and increased cholesterol: phospholipid ratio of RBC membranes. Left hemispheric chemically dominant/Pitta states had the opposite biochemical patterns. The patterns were normal or intermediate in the bihemispheric chemically dominant/ Vata state. This pattern could be correlated with various systemic and neuropsychiatric diseases and personality traits. Right hemispheric chemical dominance/Kapha state represents a hyperdigoxinemic state with membrane sodium-potassium ATPase inhibition. Left hemispheric chemical dominance/Pitta state represents the reverse pattern with hypodigoxinemia and membrane sodium-potassium ATPase stimulation. The Vata state is the intermediate bihemispheric chemical dominant state. Ninety-five percent of the patients/individuals in the tridosha, pathological, and psychological groups were right-handed/left hemispheric dominant, however, their biochemical patterns were different-either left hemispheric chemical dominant or right hemispheric chemical dominant. Hemispheric chemical dominance/tridosha states had no correlation with cerebral dominance detected by handedness/dichotic listening test[8].

There was increase in cytochrome F420 indicating archaeal growth. The archaea can synthesise and use cholesterol as a carbon and energy source[14, 15]. 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[16]. There was also an increase in archaeal HMG CoA reductase activity indicating increased cholesterol synthesis by the archaeal mevalonate pathway. The archaeal beta hydroxyl steroid dehydrogenase activity indicating digoxin synthesis and archaeal cholesterol hydroxylase activity indicating bile acid synthesis were increased[7]. The archaeal cholesterol oxidase activity was increased resulting in generation of pyruvate and hydrogen peroxide[15]. The pyruvate gets converted to glutamate and ammonia by the GABA shunt pathway. The archaeal aromatization of cholesterol generating PAH, serotonin and dopamine was also detected[17]. The archaeal glycolytic hexokinase activity and archaeal extracellular ATP synthase activity were increased. The archaea can undergo magnetite and calcium carbonate mineralization and can exist as calcified nanoforms[18]. 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 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[19]. The decrease in free self replicating RNA and DNA with the addition of antibiotics indicates that the RNA viroids are derived from archaeal introns. Archaeal pyruvate can produce histone deacetylase inhibition resulting in 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[20]. The noncoding DNA is lengthened by integrating RNA viroidal complementary DNA with the integration going on as a continuing event. The archaea genome can also get integrated into human genome using integrase as has been described for trypanosomes[21]. The integrated viroids and archaea can undergo vertical transmission and can exist as genomic parasites[20, 21]. This increases the length and alters the grammar of the noncoding region producing memes or memory of acquired characters[22]. The viroidal complementary DNA can function as jumping genes producing a dynamic genome important in storage of synaptic information, HLA gene expression and neurodevelopmental gene expression. The alteration in DNA sequences produced by viroidal complementary DNA jumping genes can lead onto schizophrenia and primary seizure disorder. The RNA viroids can regulate mRNA function by RNA interference[19]. The phenomena of RNA interference can

modulate T cell and B cell function, neuronal transmission and euchromatin/heterochromatin expression. The RNA viroid induced mRNA interference can modulate dopaminergic, glutamatergic and serotoninergic synaptic transmission. The archaea and viroidal density is high in right hemispheric dominant kapha group, intermediate in bihemispheric dominant vata group and low in left hemispheric dominant pitta group.

The presence of muramic acid, HMG CoA reductase and cholesterol oxidase activity inhibited by antibiotics indicates the presence of bacteria with mevalonate pathway. The density of the mevalonate pathway bacterial is high in right hemispheric dominant kapha state, low in left hemispheric dominant pitta state and intermediate in bihemispheric dominant vata state. The bacterial with mevalonate pathway include streptococcus, staphylococcus, actinomycetes, listeria, coxiella and borrelia[23]. The bacteria and archaea with mevalonate pathway and cholesterol catabolism had a evolutionarily advantage and constitutes the isoprenoidal clade organism with the archaea evolving into mevalonate pathway gram positive and gram negative organism through horizontal gene transfer of viroidal and virus genes[24]. The isoprenoidal clade prokaryotes develop into other groups of prokaryotes via viroidal/virus as well as eukaryotic horizontal gene transfer producing bacterial speciation[25]. The RNA viroids and its complementary DNA developed into cholesterol enveloped RNA and DNA viruses like herpes, retrovirus, influenza virus, borna virus, cytomegalo virus and Ebstein Barr virus by recombining with eukaryotic and human genes resulting in viral speciation. Bacterial and viral species are ill defined and fuzzy with all of them forming one common genetic pool with frequent horizontal gene transfer and recombination. Thus the multi and unicellular eukaryote with its genes serves the purpose of prokaryotic and viral speciation .The multicellular eukaryote developed so that their endosymbiotic archaeal colonies could survive and forage better. The multicellular eukaryotes are like bacterial biofilms. The archaea and bacteria with a mevalonate pathway uses the extracellular RNA viroids and DNA viroids for quorum sensing and in the generation of symbiotic biofilm like structures which develop into multicellular eukaryotes[26, 27]. The endosymbiotic archaea and bacteria with mevalonate pathway still uses the RNA viroids and DNA viroids for the regulation of muticellular eukaryote. Pollution is induced by the primitive nanoarchaea and mevalonate pathway bacteria synthesised PAH and methane leading on to redox stress. Redox stress leads to sodium potassium ATPase inhibition, inward movement of plasma membrane cholesterol, defective SREBP sensing, increased cholesterol synthesis and nanoarchaeal/mevalonate pathway bacterial growth[28]. Redox stress leads on to viroidal and archaeal multiplication. Redox stress can also lead to HERV reverse transcriptase and integrase expression. The noncoding DNA is formed of integrating RNA viroidal complementary DNA and archaea with the integration going on as a continuing event. The archaeal pox like dsDNA virus forms evolutionarily the nucleus. The integrated viroidal, archaeal and mevalonate pathway bacterial sequences can undergo vertical transmission and can exist as genomic parasites. The genomic integrated archaea, mevalonate pathway bacteria and viroids form a genomic reserve of bacteria and viruses which can recombine with human and eukaryotic genes producing bacterial and viral speciation. Bacteria and viruses can contribute to the regulation of hemispheric dominance and tridoshas as exemplified by schizophrenia, a disorder of consciousness. Borrelia, toxoplasma, chlamydia, mycoplasma, retroviruses, herpes virus, influenza virus and borna virus contribute to the neuropathogenesis of schizophrenia[29, 30, 31]. The change in the length and grammar of the noncoding region produces eukaryotic speciation and individuality[32]. Changes in the length of noncoding region can lead onto modulation of hemispheric dominance/tridoshas and conscious perception as exemplified in schizophrenia[33]. The human endogenous retroviruses and change in the length and grammar of the noncoding region has been described in schizophrenia. The integration of nanoarchaea, mevalonate pathway prokaryotes and viroids in to the eukaryotic and human genome produces a chimera which can multiply producing biofilm like multicellular structures having a mixed archaeal, viroidal, prokaryotic and eukaryotic characters which is a regression from the multicellular eukaryotic tissue. This results in a new neuronal, metabolic, immune and tissue phenotype producing microchimeras. Microchimeras can also generate tissue and neuronal polyploidy. The higher degree of integration of archaea, mevalonate pathway bacteria and viroids into the genome produces right hemispheric dominant kapha group, intermediate degree of integration produces bihemispheric dominant vata group and lower degree of integration left hemispheric dominant pitta group.

The archaea and viroids can regulate the nervous system including the NMDA/GABA thalamocorticothalamic pathway mediating conscious perception[2, 34]. NMDA/GABA receptors can be modulated by digoxin induced calcium oscillations resulting in NMDA/glutamic acid decarboxylase (GAD) activity induction, PAH increasing NMDA activity and inducing GAD as well as viroid induced RNA interference modulating NMDA/GABA receptors[2]. The cholesterol ring oxidase generated pyruvate can be converted by the GABA shunt pathway to glutamate and GABA. Increased NMDA transmission has been described in schizophrenia and primary seizure disorder. The dipolar 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[2, 34]. The archaea can regulate limbic lobe transmission with archaeal cholesterol aromatase/ring oxidase generated norepinephrine, dopamine, serotonin and acetyl choline[17]. Thus the shadow biosphere of archaea and viroids can regulate conscious and quantal perception. The archaea and viriods can also modulate multiple neurotransmitter systems. Schizophrenia is described as a disorder of consciousness and increased integration of archaea and viroids into the genome can contribute to its neuropathogenesis. Increased dopaminergic, serotoninergic and NMDA transmission is important in the pathogenesis of schizophrenia. The higher degree of integration of the archaea into the genome produces increased digoxin synthesis producing right hemispheric dominant kapha group and lesser degree producing left hemispheric dominant pitta group[2]. Bihemispheric dominant vata group is intermediate with normal digoxin synthesis. Right hemispheric dominant kapha group has been described in schizophrenia. The increased integration of archaea into the neuronal genome can produce increased cholesterol oxidase and aromatase mediated monoamine and NMDA transmission producing schizophrenia. The archaeal bile acids are chemically diverse and structurally different from human bile acids. The archaeal bile acids can bind olfactory GPCR receptors and stimulate the limbic lobe producing a sense of social identity. The dominance of archaeal bile acids over human bile acids in stimulating the olfactory GPCR- limbic lobe pathway leads to loss of social identity leading to schizophrenia and autism[35].

Archaea and RNA viroid can bind the TLR receptor induce NFKB producing immune activation and cytokine TNF alpha secretion. The archaeal DXP and mevalonate pathway metabolites can bind γδ TCR and digoxin induced calcium signaling can activate NFKB producing chronic immune activation[2, 36]. The archaea and viroid induced chronic immune activation and generation of superantigens can lead on to autoimmune disease. This produces a state of chronic immune activation in right hemispheric dominant kapha group producing increased predisposition to autoimmune diseases. The left hemispheric dominant pitta group is immunosuppressed and the bihemispheric dominant vata group has normal immune function.

Archaea, viroids and digoxin can induce the host AKT PI3K, AMPK, HIF alpha and NFKB producing the Warburg metabolic phenotype[37]. The increased glycolytic hexokinase activity, decrease in blood ATP, leakage of cytochrome C, increase in serum pyruvate and decrease in acetyl CoA indicates the generation of the Warburg phenotype. There is induction of glycolysis, inhibition of PDH activity and mitochondrial dysfunction resulting in inefficient energetics. The immune activation mediated increased levels of TNF alpha can produce insulin resistance acting at the level of insulin receptor. Thus a state similar to metabolic syndrome X exists in right hemispheric dominant kapha group. Left hemispheric dominant pitta group can have a pattern of increased insulin sensitivity and low body mass index producing a reverse metabolic syndrome x. The bihemispheric dominant vata state will be metabolically intermediate. Cholesterol oxidase activity, increased glycolysis related NADPH oxidase activity and mitochondrial dysfunction generates free radicals. Free radical production and mitochondrial dysfunction can increase NMDA transmission important in conscious perception. 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[37]. The increased cholesterol substrate leads to increased archaeal growth and digoxin synthesis leading to metabolic channeling to the mevalonate pathway. Hyperdigoxinemia is important in the regulation of hemispheric dominance and the tridoshas[2]. The right hemispheric dominant kapha group is hyperdigoxinemic, left hemispheric dominant pitta group is hypodigoxinemic and bihemispheric dominant vata group is normodigoxinemic. The pyruvate can be converted to glutamate and ammonia which is oxidised by archaea for energy needs. Ammonia can regulate both NMDA and GABA transmission depending on its levels.

The Warburg phenotype can contribute to the hemispheric dominance and tridoshas by augmenting the bacterial shikimic acid pathway. The upregulated glycolysis consequent to the Warburg phenotype produces phosphoenolpyruvate, a basic substrate for the bacterial shikimic acid pathway which can synthesise monoamines and neuroactive alkaloids. The shikimic acid pathway can generate dopamine and serotonin producing increased monoaminergic transmission. The shikimic acid pathway can also synthesise the neuroactive alkaloids strychnine, nicotine, morphine, mescaline and LSD important in regulating neural transmission[2]. The upregulated glycolysis can also contribute to increased NMDA and GABA transmission in the thalamocorticothalamic pathway. The glycolytic pathway produces phosphoglycerate which is converted to phosphoserine and then serine which activates the NMDA receptor. The glycolytic enzyme glyceraldehyde-3-phosphate dehydrogenase is a GABA receptor kinase and activates GABA transmission. Thus the archaea and viroid induced Warburg phenotype can contribute to the modulation of hemispheric dominance and tridoshas by regulating the multiple neurotransmitter systems. The archaeal cholesterol catabolism can deplete the cell membranes of cholesterol resulting in alteration in lipid microdomains and their related neurotransmitter receptor contributing to the regulation of NMDA, serotoninergic and dopaminergic transmission. Thus the archaeal cholesterol catabolism and viroids can regulate brain function and hemispheric dominance/tridoshas. The

archaea and viroids have axonal and transynaptic transport functioning as biological neurotransmitters. The brain can be visualized evolutionarily as a modified mevalonate pathway bacteria and archaeal colony functioning by mechanisms of quorum sensing using RNA viroids with its bacterial flagellar system forming axo-axonic and axo-dendritic connections. The third element of archaea and their derived viroids can also regulate the immune, genetic, metabolic and neural systems producing its integration.

The third element formed of intracellular archaea and viroidal symbiosis determines hemispheric dominance and tridoshas. Also archaeal cholesterol synthesis and cholesterol catabolism determines hemispheric dominance and tridoshas.

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