# **Chapter 2**

## Archaeal Digoxin Mediated Model for Sexual Orientation

### Introduction

Global warming induces a genomic change in humans. Global warming induces endosymbiotic archaeal and RNA viroidal growth. The porphyrins form a template for the formation of RNA viroids, DNA viroids, prions, isoprenoids and polysaccharides. They can symbiose together to form primitive archaea. The archaea can further induce HIF alpha, aldose reductose and fructolysis resulting in further porphyrinogenesis and archaeal self replication. The primitive archaeal DNA is integrated along with RNA viroids which are converted to their corresponding DNA by the action of redox stress induced HERV reverse transcriptase into the human genome by the redox stress induced HERV integrase. The archaeal DNA sequences that are integrated into the human genome forms endogenous archaeal human genomic sequences akin to HERV sequences and can function as jumping genes regulating genomic DNA flexibility. The integrated endogenous genomic archaeal sequences can get expressed in the presence of redox stress forming endosymbiotic archaeal particles which can function as a new organelle called the archaeaons. The archaeaon can express the fructolytic pathway constituting an organelle called the fructosome, cholesterol catabolic pathway and digoxin synthetic forming an organelle called the steroidelle, the shikimic acid pathway forming an organelle called the neurotransminoid, antioxidant vitamin E and vitamin C synthetic organelle called the vitaminocyte as well as the glycosaminoglycan synthetic organelle called glycosaminoglycoid. The archaeaon secreting RNA viroids is called the viroidelle.

Thus the actinidic archaeal symbiosis results in neanderthalisation of the population and generation of androgyny. The actinidic archaeal overgrowth and symbiosis is a consequence of global warming. Archaea are extremophiles and increase in density during periods of climate change. The actinidic archaeal catabolism of cholesterol generates digoxin and increased intracellular calcium resulting in formation of excess of gasotransmitters important in autonomic function of structures like the corpora cavernosa. The cholesterol catabolism results in depletion of cholesterol and to a state of lack of sex hormone synthesis. This produces an asexual state resulting in a social system of matriarchy related to androgyny. The actinidic archaeal cholesterol catabolism generates porphyrins producing the extrasensory quantal perceptive state associated with androgyny. This contributes to the creativity of the androgynous state. The porphyrin synthesis associated with androgyny also contributes to the disease states associated with it. This includes autoimmune disease, cancer, degenerations, acquired immunodeficiency syndrome, metabolic syndrome X and all civilisational disease.

The increase in endogenous EDLF, a potent inhibitor of membrane  $Na^+-K^+$ ATPase, can decrease this enzyme activity. The results showed increased endogenous EDLF synthesis as evidenced by increased HMG CoA reductase activity, which functions as the rate limiting step of the isoprenoid pathway. Studies in our laboratory have demonstrated that EDLF is synthesized by the isoprenoid pathway. The endosymbiotic archaeal sequences in the human genome get expressed by redox stress and osmotic stress of global warming. This results in induction of HIF alpha which will upregulate fructolysis and glycolysis. In the setting of redox stress all glucose gets converted to fructose by the induction of enzymes aldose reductase and sorbitol dehydrogenase. Aldose reductase converts glucose to sorbitol and sorbitol dehydrogenase converts sorbitol to fructose. Since fructose is preferentially phosphorylated by ketohexokinases the cell is depleted of ATP and glucose phosphorylation comes to a halt. Fructose becomes the dominant sugar that is metabolized by fructolysis in expressed archaeal particles in the cell functioning as organelle called fructosoids. The fructose is phosphorylated to fructose 1-phosphate which is acted upon by aldolase B which converts it into glyceraldehyde

3-phosphate and dihydroxy acetone phosphate. Glyceraldehyde 3-phosphate is converted to D 1,3-biphosphoglycerate which is then converted to 3-phosphoglycerate. The 3-phosphoglycerate is converted to 2-phosphoglycerate. 2-phosphoglycerate is converted to phosphoenol pyruvate by the enzyme enolase. Phosphoenol pyruvate is converted to pyruvate by the enzyme pyruvic kinase. The archaeaon induces HIF alpha which upregulates fructolysis and glycolysis but inhibits pyruvate dehydrogenase. The forward metabolism of pyruvate is stopped. The dephosphorylation of phosphoenol pyruvate is inhibited in the setting of pyruvic kinase inhibition. Phosphoenol pyruvate enters the shikimic acid pathway where it is converted to chorismate. The shikimic acid is synthesized by a pathway starting from glyceraldehyde 3-phosphate. Glyceraldehyde 3-phosphate combines with the pentose phosphate pathway metabolite sedoheptulose 7-phosphate which is converted to erythrose 4-phosphate. The pentose phosphate pathway is upregulated in the presence of the suppression of glycolytic pathway. Erythrose 4-phosphate combines with phosphoenol pyruvate to generate shikimic acid. Shikimic acid combines with another molecule of phosphoenol pyruvate to generate chorismate. The chorismate is converted to prephenic acid and then to parahydroxy phenyl pyruvic acid. Parahydroxy phenyl pyruvic acid is converted to tyrosine and tryptophan as well as neuroactive alkaloids. The shikimic acid pathway is structured in expressed archaeaon organelle called the neurotransminoid. The fructolytic intermediates glyceraldehydes 3-phosphate and pyruvate are the starting points of the DXP pathway of cholesterol synthesis. Glyceraldehyde 3-phosphate combines with pyruvate to form 1-deoxy D-xylulose phosphate (DOXP) which is then converted to 2-C methyl erythritol phosphate. 2-C methyl erythritol phosphate can be synthesized from erythrose 4-phosphate a metabolite of the shikimic acid pathway. DXP combines with MEP to form isopentenyl pyrophosphate which is converted to cholesterol. Cholesterol is

catabolized by archaeal cholesterol oxidases to generate digoxin. The digoxin sugars digitoxose and rhamnose are synthesized by the upregulated pentose phosphate pathway. Glycolytic suppression leads to upregulation of the pentose phosphate pathway. The expressed archaeaon organelle concerned with cholesterol catabolism and digoxin synthesis is called the steroidelle. The suppression of glycolysis and stimulation of fructolysis results in upregulation of the hexosamine pathway. Fructose is converted to fructose 6-phosphate by ketohexokinases. The fructose 6-phosphate is converted to glucosamine 6-phosphate by the action of glutamine fructose 6-phosphate amidotransferase (GFAT). Glucosamine 6-phosphate is converted to UDP N-acetyl glucosamine which is then converted to N-acetyl glucosamine and various amino sugars. UDP glucose is converted to UDP D-glucuronic acid. UDP D-glucuronic acid is converted to glucuronic acid. This forms the uronic acid synthetic pathway. Uronic acids and hexosamines form repeating units of glycosaminoglycans. In the setting of glycolytic suppression and fructolytic metabolism fructolysis leads to increase synthesis of hexosamines and GAG synthesis. The GAG synthesizing archaeaon particles are called the glycosaminoglycoids. The expressed archaeaon particles are capable of synthesizing antioxidant vitamin C and E. The UDP D-glucose is converted to UDP D-glucuronic acid. UDP D-glucuronic acid is converted to D-glucuronic acid. D-glucuronic acid is converted to L-gulonate by enzyme aldoketoreductases. L-gulonate is converted to L-gulonolactone by lactonase. L-gulonolactone is converted to ascorbic acid by the action of archaeal L-gulo oxidase. The vitamin E is synthesized from shikimate which is converted to tyrosine and then to parahydroxy phenyl pyruvic acid. Parahydroxy phenyl pyruvic acid is converted to homogentisate. Homogentisate is converted to 2-methyl 6-phytyl benzoquinone which is converted to alpha tocopherol. 2-methyl 6-phytyl benzoquinone is converted to 2,3-methyl 6-phytyl benzoquinone and gamma tocopherol. Vitamin E can also



be synthesized by the DXP pathway. Glyceraldehyde 3-phosphate and pyruvate combined to form 1-deoxy D-xylulose 5-phosphate which is converted to 3-isopentenyl pyrophosphate. 3-isopentenyl pyrophosphate and dimethyl allyl pyrophosphate combined to form 2-methyl 6-phytyl benzoquinone which is converted to tocopherols. The ubiquinone another important membrane antioxidant and part of the mitochondrial electron transport chain is synthesized by the shikimic acid pathway and DXP pathway. The isoprenoid moiety of ubiquinone is contributed from the DXP pathway and the rest of it by tyrosine catabolism. The tyrosine is generated by the shikimic acid pathway. The archaeaon particles concerned with the synthesis of vitamin C, vitamin E and ubiquinone which are all antioxidants are called the vitaminocyte.

The human hypothalamus produces an endogenous membrane  $Na^+-K^+$ ATPase inhibitor, digoxin. Membrane  $Na^+-K^+$  ATPase inhibition can lead on to an increase in intracellular calcium and reduction in intracellular magnesium. Intracellular calcium can induce the enzyme nitric oxide synthase. Nitric oxide synthase is the key enzyme regulating nitric oxide synthesis. Nitric oxide is an important neurotransmitter in mediating erection. Digoxin can also regulate amino acid and neurotransmitter transport. Hypothalamic structural defects had earlier been documented in the homosexual population.

It was therefore considered pertinent to study the digoxin status, neurotransmitter patterns and nitric oxide synthesis in people with different sexual orientation. The patterns were compared with those obtained in patients with right hemispheric, left hemispheric and bihemispheric dominance to find out whether hemispheric dominance has any correlation with sexual orientation. The results are presented in this paper.

### Results

- (1) The results showed that HMG CoA reductase activity and serum digoxin were increased in homosexuals, promiscuous heterosexuals and bisexuals indicating upregulation of the isoprenoid pathway but RBC membrane sodium-potassium ATPase activity and serum magnesium were reduced. In non-promiscuous heterosexuals, HMG CoA reductase activity and serum digoxin were reduced while RBC membrane Na<sup>+</sup>-K<sup>+</sup> ATPase activity and serum magnesium were increased.
- (2) The results showed that the concentration of tryptophan, quinolinic acid and serotonin was found to be higher in the plasma of homosexuals, bisexuals and promiscuous heterosexuals while that of tyrosine, dopaminc and norepinephrine was lower. Serum of these patients contained high levels of strychnine and nicotine but no morphine was detected. In non-promiscuous heterosexuals the serum levels of tryptophan, serotonin, quinolinic acid, strychnine and nicotine were reduced while that of tyrosine, dopamine and morphine were increased.
- (3) There was increase in nitric oxide levels in homosexuals, promiscuous heterosexuals and bisexuals. In non-promiscuous heterosexuals serum nitric oxide levels were low.
- (4) The results showed that HMG CoA reductase activity and serum digoxin were increased in left-handed/right hemispheric dominant individuals. The results also showed that HMG COA reductase activity and serum digoxin were decreased in right handed / left hemispheric dominant individuals. The results showed that the concentration of tryptophan, quinolinic acid serotonin, strychnine and nicotine was found to be higher in the plasma of left handed / right hemispheric dominant individuals while that of tyrosine, dopamine, morphine and norepinephrine was lower. The results also



showed that the concentration of tryptophan, quinolinic acid serotonin, strychnine and nicotine was found to be lower in the plasma of right handed / left hemispheric dominant individuals while that of tyrosine, dopamine, morphine and norepinephrine was higher.

### Discussion

## Archaeal Digoxin and Membrane Na<sup>+</sup>-K<sup>+</sup> ATPase Inhibition in Relation to Sexual Orientation

The archaeaon steroidelle DXP pathway and the upregulated pentose phosphate pathway contribute to digoxin synthesis. The increase in endogenous digoxin, a potent inhibitor of membrane Na<sup>+</sup>-K<sup>+</sup> ATPase can decrease this enzyme activity. In homosexuals, promiscuous heterosexuals and bisexuals there was significant inhibition of the RBC membrane Na<sup>+</sup>-K<sup>+</sup> ATPase and this inhibition appears to be a common feature in these groups. There was increased synthesis of digoxin as evidenced by increased HMG CoA reductase activity. Studies have shown that endogenous digoxin is synthesized by the isoprenoid pathway. The inhibition of  $Na^+-K^+$  ATPase by digoxin is known to cause an increase in intracellular calcium resulting from increased Na<sup>+</sup>-Ca<sup>++</sup> exchange, increased entry of calcium via the voltage gated calcium channel and increased release of calcium from intracellular endoplasmic reticulum calcium stores. This increase in intracellular calcium by displacing magnesium from its binding sites, causes a decrease in the functional availability of magnesium. This decrease in the availability of magnesium can cause decreased mitochondrial ATP formation which along with low magnesium can cause further inhibition of  $Na^+-K^+$  ATPase, since ATP-magnesium complex is the actual substrate for this reaction. Cytosolic free calcium is normally buffered by two mechanisms, ATP dependent calcium extrusion from cell and ATP dependent sequestration of calcium within the endoplasmic reticulum. The magnesium depletion related

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mitochondrial dysfunction results in defective calcium extrusion from the cell. There is thus a progressive inhibition of Na<sup>+</sup>-K<sup>+</sup> ATPase activity first triggered by digoxin. Low intracellular magnesium and high intracellular calcium consequent to Na<sup>+</sup>-K<sup>+</sup> ATPase inhibition appear to be crucial to the pathophysiology of homosexuality, bisexuality and heterosexual promicuousity. The intracellular positive Ca<sup>++</sup> signal and negative Mg<sup>++</sup> signal can regulate diverse cellular process. Ca<sup>++</sup> on entry into the cell is used to charge up the endoplasmic reticulum stores which then release a burst of signal calcium responsible for activating a large variety of calcium dependent cellular processes. The information processing capability of the calcium signalling system is enhanced by amplitude and frequency modulation. The Ca<sup>++</sup> is released from channels on internal ER individually or in small groups (blip/quark and puffs/sparks). Further diversity of calcium signalling is produced by compartmentalization as cytosolic calcium signal and nuclear calcium signal. Serum magnesium was assessed in homosexuality, bisexuality and heterosexual promicuousity and was found to be reduced.

The decrease in the activity of HMG CoA reductase in heterosexual non-promiscuous individuals suggests a downregulation of the isoprenoid pathway. There is a marked decrease in plasma digoxin and this decrease may be a consequence of decreased channelling of intermediates of the isoprenoid pathway for its biosynthesis. The decrease in endogenous digoxin, a potent inhibitor of membrane of Na<sup>+</sup>-K<sup>+</sup> ATPase, can increase this enzyme activity. In non-promiscuous heterosexuals there was significant stimulation of the RBC membrane of Na<sup>+</sup>-K<sup>+</sup> ATPase. The stimulation of Na<sup>+</sup>-K<sup>+</sup> ATPase by digoxin is known to cause a decrease in intracellular calcium resulting from decreased Na<sup>+</sup>-Ca<sup>++</sup> exchange, decreased entry of calcium via the voltage gated calcium channel and decreased release of calcium from intracellular endoplasmic reticulum calcium stores. This decrease in intracellular calcium by not



displacing magnesium from its binding sites causes an increase in the functional availability of magnesium. This increase in the availability of magnesium can cause increased mitochondrial ATP formation which along with increased magnesium can cause further stimulation of  $Na^+-K^+$  ATPase, since ATP-magnesium complex is the actual substrate for this reaction. There is thus a progressive stimulation of  $Na^+-K^+$  ATPase activity. The increased intracellular magnesium related mitochondrial ATP synthesis results in increased calcium extrusion from the cell. High intracellular magnesium and low intracellular calcium consequent to  $Na^+-K^+$  ATPase stimulation appear to be crucial to the pathophysiology of heterosexual non-promiscuousity. Serum magnesium was assessed in non-promiscuous heterosexuals and was found to be increased.

#### Archaeal Digoxin and Regulation of Neurotransmitter Synthesis and Function in Relation to Sexual Orientation

The archaeaon neurotransminoid shikimic acid pathway contributes to tryptophan and tyrosine synthesis and catabolism generating neurotransmitters and neuroactive alkaloids. There is an increase in tryptophan and its catabolites and reduction in tyrosine and its catabolites in the serum of homosexuals, bisexuals and promiscuous heterosexuals. This could be due to the fact that digoxin can regulate neutral amino acid transport system with preferential promotion of tryptophan transport over tyrosine. In the presence of hypomagnesemia, the magnesium block on the NMDA receptor is removed leading to NMDA excitotoxicity. The increased presynaptic neuronal calcium can produce cyclic AMP dependent phosphorylation of synapsins resulting in increased neurotransmitter release into the synaptic junction and vesicular recycling. Increased intracellular calcium in the post synaptic neuron can also activate the calcium dependent NMDA signal transduction. The plasma membrane neurotransmitter transporter (on the surface of the glial cell and

presynaptic neuron) is coupled to a sodium gradient which is disrupted by the inhibition of Na<sup>+</sup>-K<sup>+</sup> ATPase, resulting in decreased clearance of glutamate by presynaptic and glial uptake at the end of synaptic transmission. By these mechanisms, inhibition Na<sup>+</sup>-K<sup>+</sup> ATPase can promote glutamatergic transmission. The elevated levels of quinolinic acid, strychnine and serotonin can also contribute to NMDA excitotoxicity. Strychnine displaces glycine from its binding sites and inhibits glycinergic inhibitory transmission in the brain. The glycine is free to bind to the strychnine insensitive site of the NMDA receptor and promote excitatory NMDA transmission. Quinolinic acid and serotonin are also positive modulators of the NMDA receptor. NMDA excitotoxic mechanisms can lead on to increased generation of nitric oxide by induction of nitric oxide synthase in the post synaptic neuron consequent to leakage of calcium into the cell. The decrease in membrane Na<sup>+</sup>-K<sup>+</sup> ATPase activity in homosexuals, bisexuals and promiscuous hexterosexuals could be due to the fact that the hyperpolarising neurotransmitters (dopamine, morphine and noredrenaline) are reduced and the depolarising neuroactive compounds (serotonin, glutamate, strychnine, nicotine and quinolinic acid) are increased.

The schizoid neurotransmitter pattern of reduced dopamine, noradrenaline and morphine and increased serotonin, strychnine and nicotine is common to homosexuals, bisexuals and promiscuous heterosexuals and could predispose to their development. Quinolinic acid, an NMDA agonist can contribute to NMDA excitotoxicity reported in schizophrenia. Strychnine by blocking glycinergic transmission can contribute to the decreased inhibitory transmission in schizophrenia. Recent data suggest that the initial abnormality in schizophrenia involves a hypodopaminergic state and the low dopamine levels now observed agrees with this. Nicotine by interacting with nicotinic receptors can facilitate the release of dopamine, promoting the dopaminergic transmission in the brain. This can explain the increased dopaminergic transmission in the presence of



decreased dopamine levels. The increased serotoniriergic activity and reduced noradrenergic outflow from locus coreuleus reported earlier h schizophrenia agrees with our finding of elevated serotonin and reduced noradrenaline levels. A schizoid type of personality could predispose to the development of homosexuality, bisexuality and heterosexual promiscuity.

The concentration of tryptophan, quinolinic acid and serotonin was found to be lower in the plasma of non-promiscuous heterosexuals while that of tyrosine, dopamine, morphine and norepinephrine was higher. Thus there is a decrease in tryptophan and its catabolites and a increase in tyrosine and its catabolites in the patient's serum. This could be due to the fact digoxin can regulate neutral amino acid transport system with preferential promotion of tryptophan transport over tyrosine and that digoxin levels are low in non-promiscuous heterosexuals. The increased level of morphine in non-promiscuous heterosexuals is also significant. The low level of quinolinic acid, serotonin and strychnine can contribute to reduced excitatory glutamatergic transmission as they are all positive modulators of the NMDA receptor. In the presence of hypermagnesemia, the magnesium block on the NMDA receptors is strengthened leading on to reduced NMDA transmission. The decreased presynaptic neuronal calcium can produce reduced cyclic AMP dependent dephosphorylation of synapsins resulting in decreased glutamate release into the synaptic junction and vesicular recycling. Decreased intracellular calcium in the post synaptic neuron can also inhibit the calcium dependent NMDA signal transduction. The plasma membrane glutamate transporter (on the surface of the glial cell and presynaptic neuron) is coupled to a sodium gradient which is activated by the stimulation of Na<sup>+</sup>-K<sup>+</sup> ATPase, resulting in increased clearance of glutamate by presynaptic and glial uptake at the end of synaptic transmission. By these mechanisms, stimulation of Na<sup>+</sup>-K<sup>+</sup> ATPase can inhibit glutamatergic transmission. Decreased glutamatergic transmission leads to reduced generation

of nitric oxide. The increase in membrane  $Na^+-K^+$  ATPase activity in non-promiscuous heterosexuals could be due to the fact that the hyperpolarising neurotransmitters (dopamine, morphine and noradrenaline) are increased and the depolarising neuroactive compounds (serotonin, strychnine, nicotine, quinolinic acid and glutamate) are decreased. Decreased serotonin can lead on to depression and obsessive neurosis. Such a psychopathology can lead on to heterosexuals non-promiscuity.

Membrane  $Na^+-K^+$  ATPase inhibition leads to an increase in intracellular calcium. This leads on to induction of nitric oxide synthase and generation of nitric oxide. Nitric oxide mediates penile erection. There is increased level of nitric oxide in homosexuals, bisexuals and promiscuous heterosexuals. The level of nitric oxide is low in heterosexual non - promiscuous males. This is due to membrane  $Na^+-K^+$  ATPase stimulation and reduction in intracellular calcium in heterosexual non-promiscuous males.

## Archaeal Digoxin and Hemispheric Dominance in Relation to Sexual Orientation

The archaeaon related organelle-steroidelle, neurotransminoid and vitaminocyte contribute to hemispheric dominance. The chemical patterns obtained in right hemispheric chemical dominance are hyperdigoxinemia, increased tryptophan catabolites and reduced tyrosine catabolites. This corresponds with the pattern obtained in homosexuality, bisexuality and heterosexual promiscuity. The chemical patterns obtained in left hemispheric chemical dominance are hypodigoxinemia, reduced tryptophan catabolites and increased tyrosine catabolites. This corresponds with the pattern obtained in heterosexual non-promiscuity. Thus sexual orientation is determined by hemispheric dominance and digoxin status. Hemispheric dominance has been reported earlier to be associated with psychological and physiological states. We have earlier reported on hyperdigoxinemia and an upregulated isoprenoid pathway in the acquired immunodeficiency syndrome. The fact that sexual orientation could also be related to digoxin status has a bearing on the pathogenesis of the acquired immunodeficiency syndrome.

### References

[1] Kurup RK, Kurup PA. *Hypothalamic Digoxin, Cerebral Dominance and Brain Function in Health and Diseases.* New York: Nova Medical Books, 2009.

