# Chapter 9

## Archaeal Digoxin, Regulation of Neuronal Transmission and Cerebral Dominance

## Introduction

There is a specialisation of function in the right and left hemispheres of the brain as manifested in cognitive dysfunctions noticed in lesions of the same. Typical cerebral lateralization is associated with left cerebral dominance for language, praxis and serial processing, whereas the right cerebral hemisphere is dominant for externally directed attention, visuospatial tasks and gestalt processing. The right hemisphere is also dominant for emotional stimuli, and patients with right cerebral lesions may exhibit hypoarousal and emotional indifference. There is no data as of now on neurotransmitter differences between right and left hemispheres though functional differences have been noticed as described above. The human hypothalamus synthesizes an endogenous membrane $Na^+$-$K^+$ ATPase inhibitor, digoxin by the isoprenoid pathway. Since digoxin can regulate multiple neurotransmitter systems, it could play a role in the genesis of cerebral dominance. The present study assessed the changes in the synthesis of an endogenous membrane $Na^+$-$K^+$ ATPase inhibitor, archaeal digoxin and neurotransmitter changes in right and left handed individuals and their relationship to cerebral dominance. The results are presented in this paper.

## Results

(1) The results showed that HMG CoA reductase activity and serum digoxin were increased in left handed / right hemispheric dominant individuals while RBC membrane $Na^+$-$K^+$ ATPase and serum magnesium were decreased. The results also showed that HMG CoA reductase activity and serum digoxin were decreased while RBC membrane $Na^+$-$K^+$ ATPase and serum magnesium were increased in right handed / left hemispheric dominant individuals.

(2) 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. There was an increase in NO in left handed / right hemispheric dominant individuals. There was decrease in NO in right handed / left hemispheric dominant individuals.

## Discussion

$Na^+$-$K^+$ ATPase is an active transport system present in the cell membrane of nearly all animal cells. This enzyme is particularly important in the brain because about 2/3 of the energy demand of this organ is used to maintain the characteristic transmembrane potential across the neuronal membrane by the action of $Na^+$-$K^+$ ATPase.

$Na^+$-$K^+$ ATPase contains two sub units, α and β. The α sub unit contains the catablytic site for ATP hydrolysis and for digoxin binding. There are three types of α sub units, $\alpha_1$ which is widely distributed and is digoxin resistant, $\alpha_2$ and $\alpha_3$ are digoxin sensitive and are restricted to the excitable tissues. $\alpha_3$ the predominant subunit is neuron while $\alpha_2$ is predominant in the muscle, heart and glial cell. The three subunits which are glycosylated polypeptides also exist in two forms $\beta_1$ and $\beta_2$. One isoform of $\beta_2$ (AMOG) is the adhesion molecule of the glial cell. This isoform promotes neuritic outgrowth and neuronal migration. Thus normal functioning of $Na^+$-$K^+$ ATPase is important for neuronal function.

In recent reports on endogenous digoxin, a potent inhibitor of $Na^+$-$K^+$ ATPase was synthesized by the hypothalamus. The increase in endogenous digoxin, a

potent inhibitor or membrane $Na^{+}$-$K^{+}$ ATPase, can decrease this enzyme activity in left handed / right hemispheric dominant individuals. In left handed / right hemispheric dominant there was significant inhibition of the RBC membrane $Na^{+}$-$K^{+}$ ATPase. The inhibition of $Na^{+}$-$K^{+}$ ATPase by digoxin is known to cause an increase in intracellular calcium resulting from increased $Na^{+}$-$Ca^{++}$ 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 related mitochondrial dysfunction results in defective calcium extrusion from the cell. There is thus a progressive inhibition of $Na^{+}$-$K^{+}$ ATPase activity first triggered by digoxin. Low intracellular magnesium and high intracellular calcium consequent to $Na^{+}$-$K^{+}$ ATPase inhibition is seen in right hemispheric dominant / left handed individuals. There is evidence for increased digoxin synthesis in left handed / right hemispheric dominant individuals from the increase in HMG CoA reductase in activity that is noticed. HMG CoA reductase is the rate limiting enzymes of the isoprenoid pathway. In this connection, incorporation of $^{14}$C-acetate into digoxin in rat brain has been shown by us indicating that acetyl CoA is the precursor for digoxin biosynthesis in mammals also. Serum magnesium was assessed in left handed / right hemispheric dominant individuals and was found to be reduced.

The decrease in the activity of HMQ CoA reductase in right handed individuals / left hemispheric dominant suggested a downregulation of the isoprenoid pathway. There is a marked decrease in plasma digoxin levels. The decrease in endogenous digoxin, a potent inhibitor of membrane $Na^+$-$K^+$ ATPase, can increase this enzyme activity. In right handed / left hemispheric dominant individuals there was significant stimulation of the RBC membrane $Na^+$-$K^+$ ATPase. The stimulation of $Na^+$-$K^+$ ATPase by a decrease in digoxin synthesis is known to cause a decrease in intracellular calcium resulting from decreased $Na^+$-$Ca^{++}$ exchange, decreased entry of calcium via the voltage gated calcium channel and decreased release of calcium from intracellular endoplasmic reticulum calcium stores. 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 increased intracellular magnesium related mitochondrial ATP synthesis resulted in increased calcium extrusion from the cell. There is thus a progressive stimulation of $Na^+$-$K^+$ ATPase activity. High intracellular magnesium and low intracellular calcium consequent to $Na^+$-$K^+$ ATPase stimulation is seen in right handed left hemispheric dominant individuals. Serum magnesium was assessed in right handed / left hemispheric dominant individuals and was found to be increased.

There was an increase in tryptophan and its catabolites and a reduction in tyrosine and its catabolites in the serum of left handed / right hemispheric dominant individuals. This could be due to the fact that digoxin can regulate a neutral amino acid transport system with preferential promotion of tryptophan transport over tyrosine. The decrease in membrane $Na^+$-$K^+$ ATPase activity in left handed / right hemispheric dominant individuals could be due to the fact that the hyperpolarising neurotransmitters (dopamine, morphine and noradrenaline) are reduced and the depolarising neuroactive compounds (serotonin, strychnine, nicotine and quinolinic acid) are increased. Studies from

our laboratory have demonstrated the synthesis of endogenous nicotine and strychnine from tryptophan and endogenous morphine from 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 an increased neurotransmitter release into the synaptic junction and vesicular recycling. Increased intracellular calcium in the postsynaptic neuron can also activate the calcium dependent NMDA signal transduction. The plasma membrane neurotransmitter transporter (on the surface of the gilal cell and presynaptic neuron) is coupled to a sodium gradient which is disrupted by the inhibition of $Na^+$-$K^+$ ATPase, resulting in decreased clearance of glutamate by presynaptic and glial uptake at the end of synaptic transmission. By these mechanisms, inhibition $Na^+$-$K^+$ 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. Nicotine binds to the central nicotinic cholinergic receptor promoting cholinergic transmission in the brain. There was increased production of nitric oxide in hyperdigoxinemic individuals consequent to induction of nitric oxide synthase by increased intracellular calcium. Thus in the right hemisphere dominant hyperdigoxinemic state there is upregulated serotoninergic, cholinergic, NO and glutamatergic transmission and downregulated doparninergic, glycinergic and noradrenergic transmission.

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

dopamine and norepinephrine was higher. Thus there is a decrease in tryptophan and its catabolites and an increase in tyrosine and its catabolites in the serum of right handed / left hemispheric dominant individuals. 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 right handed / left hemispheric dominant individuals. The increase in membrane $Na^+$-$K^+$ ATPase activity in these cases could be due to the fact that the hyperpolarising neurotransmitters (dopamine, morphine and noradrenaline) are increased and the depolarising neuroactive compounds (serotonin, strychnine, nicotine and quinolinic acid) are decreased. 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 receptor is strengthened leading on to reduced NMDA transmission. The decreased presynaptic neuronal calcium can produce reduced cyclic AMP dependent phosphorylation of synapsins resulting in decreased in glutamate release into the synaptic junction and vesicular recycling. The plasma membrane glutamate transporter (on the surface of the glial cell and presynaptic neuron) is coupled to sodium gradient which is activated by the stimulation of $Na^+$-$K^+$ ATPase, resulting in increased clearance of glutamate by presynaptic and glial uptake at the end of synaptic transmission. By these mechanisms, stimulation of $Na^+$-$K^+$ ATPase can inhibit glutamatergic transmission. Low levels of nicotine in left hemispheric dominant individuals can downregulate cholinergic transmission. Decreased production of nitric oxide occurs in right handed / left hemispheric dominant individuals consequent to inhibition of nitric oxide synthase by the reduced intracellular calcium levels. Thus in the left hemisphere dominant hypodigoxinemic state there is downregulated serotoninergic, cholinergic, NO and glutamatergic transmission and upregulated

dopaminergic, glycinergic and noradrenergic transmission. Thus hypothalamic archaeal digoxin can play a crucial role in the genesis of cerebral dominance and regulation of neuronal transmission.

## References

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