

# **Chapter 5**

Archaeal Digoxin, Cerebral Dominance and  
Membrane Biochemistry

## 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 isoprenoid pathway is a key regulatory pathway in the cell. It produces digoxin (an endogenous membrane  $\text{Na}^+\text{-K}^+$  ATPase inhibitor), dolichol (important in N-glycosylation of proteins), ubiquinone (component of the mitochondrial electron transport chain) and cholesterol (a component of cellular membranes). Since digoxin can regulate multiple neurotransmitter systems it could possibly play a role in the genesis of cerebral dominance. Cerebral dominance could also possibly influence cellular structure and function through changes in the isoprenoid pathway. The present study assessed the changes in the synthesis of an endogenous membrane  $\text{Na}^+\text{-K}^+$  ATPase inhibitor, archaeal digoxin and changes in membrane structure / function in right hemispheric dominant and left hemispheric dominant individuals. The results are presented in this paper.

## Results

The results showed that HMG CoA reductase activity and serum digoxin were increased and RBC membrane  $\text{Na}^+\text{-K}^+$  ATPase activity and serum magnesium were reduced in left handed / right hemispheric dominant individuals. The results also showed that HMG CoA reductase activity and serum digoxin were decreased and RBC membrane  $\text{Na}^+\text{-K}^+$  ATPase activity and serum magnesium were increased in right handed / left hemispheric dominant individuals.

The cholesterol: phospholipid ratio of the RBC membrane was increased in left handed / right hemispheric dominant individuals. The concentration of total GAG, hexose and fucose of glycoprotein decreased in the RBC membrane and increased in the serum suggesting their reduced incorporation into the membrane and defective membrane formation in left handed / right hemispheric dominant individuals. The cholesterol: phospholipid ratio of the RBC membrane was decreased in right handed / left hemispheric dominant individuals. The concentration of total GAG, hexose and fucose of glycoprotein increased in the RBC membrane and decreased in the serum suggesting their increased incorporation into the membrane and defective membrane formation in right handed / left hemispheric dominant individuals.

## Discussion

### Archaeal Digoxin Synthesis / Hemispheric Dominance

There are recent reports on endogenous digoxin, a potent inhibitor of  $\text{Na}^+\text{-K}^+$  ATPase synthesized by the hypothalamus. The increase in endogenous digoxin, a potent inhibitor of membrane  $\text{Na}^+\text{-K}^+$  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  $\text{Na}^+\text{-K}^+$  ATPase. The inhibition of  $\text{Na}^+\text{-K}^+$  ATPase by digoxin is known to cause an increase in intracellular calcium resulting from increased  $\text{Na}^+\text{-Ca}^{++}$  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  $\text{Na}^+\text{-K}^+$  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  $\text{Na}^+\text{-K}^+$  ATPase activity first triggered by digoxin. Low intracellular magnesium and high intracellular calcium consequent to  $\text{Na}^+\text{-K}^+$  ATPase inhibition is seen in right hemispheric dominant / left handed individuals. The intracellular positive calcium signal and negative magnesium signal can regulate diverse cellular process. Calcium on entry into the cell is used to charge up the internal 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 calcium is released from channels on internal ER individually or in small groups (hip/quark and puffs/sparks). Further diversity of calcium signalling is produced by compartmentalization as cytosolic calcium signal and nuclear calcium signal. 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  $^{14}\text{C}$ -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 HMG CoA reductase in right handed individuals / left hemispheric dominant suggesting a downregulation of the isoprenoid pathway. There is a marked decrease in plasma digoxin levels

consequent to its reduced synthesis in left hemispheric dominant state. The decrease in endogenous digoxin, a potent inhibitor of membrane  $\text{Na}^+\text{-K}^+$  ATPase, can increase this enzyme activity. In right handed / left hemispheric dominant individuals there was significant stimulation of the RBC membrane  $\text{Na}^+\text{-K}^+$  ATPase. The stimulation of  $\text{Na}^+\text{-K}^+$  ATPase by decrease in digoxin synthesis is known to cause a decrease in intracellular calcium resulting from decreased  $\text{Na}^+\text{-Ca}^{++}$  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 results in increased calcium extrusion from the cell. There is thus a progressive stimulation of  $\text{Na}^+\text{-K}^+$  ATPase activity. High intracellular magnesium and low intracellular calcium consequent to  $\text{Na}^+\text{-K}^+$  ATPase stimulation is seen in right handed left hemispheric dominant individuals. The intracellular negative calcium signal and positive magnesium signal can regulate diverse cellular process. Serum magnesium was assessed in right handed / left hemispheric dominant individuals and was found to be increased.

### **Archaeal Digoxin, Cerebral Dominance and Membrane Structure / Function**

The alteration in the isoprenoid pathway specifically, cholesterol as well as changes in glycoproteins and GAG can affect cellular membranes. The upregulation of the isoprenoid pathway in the right hemispheric dominant state can lead to increased cholesterol synthesis and magnesium deficiency can inhibit phospholipid synthesis. Phospholipid degradation is increased due to increase in intracellular calcium activating phospholipase  $\text{A}_2$  and D. The cholesterol: phospholipid ratio of the RBC membrane was increased in the right

hemispheric dominant state. The concentration of total GAG, hexose and fucose of glycoprotein decreased in the RBC membrane and increased in the serum suggesting their reduced incorporation into the membrane and defective membrane formation. The glycoproteins, GAG and glycolipids of the cellular membrane are formed in the endoplasmic reticulum, which is then budded off as a vesicle, which fuses with the golgi complex. The glycoconjugates are then transported via the golgi channel and the golgi vesicle fuses with the cell membrane. This trafficking depends upon GTPases and lipid kinases, which are crucially dependent on magnesium and are defective in magnesium deficiency. The change in membrane structure produced by alteration in glycoconjugates and the cholesterol: phospholipid ratio can produce changes in the conformation  $\text{Na}^+ - \text{K}^+$  ATPase resulting in further membrane  $\text{Na}^+ - \text{K}^+$  ATPase inhibition. The same changes can affect the structure of organelle membrane. This results in defective lysosomal stability and leakage of glycohydrolases and GAG degrading enzymes into the serum. Defective peroxisomal membranes lead to catalase dysfunction which has been documented in right hemispheric dominant individuals. Thus in the hyperdigoxinemic right hemisphere dominant state there is defective membrane formation, membrane structure and function.

The downregulation of the isoprenoid pathway in right handed / left hemispheric dominant individuals can lead to decreased cholesterol synthesis and magnesium excess can stimulate phospholipid synthesis. Phospholipid degradation is decreased owing to decrease in intracellular calcium inhibiting phospholipase  $\text{A}_2$  and D. The cholesterol: phospholipid ratio of the RBC membrane was decreased in hypodigoxinemia. The concentration of total GAG, hexose and fucose of glycoprotein increased in the RBC membrane and decreased in the serum suggesting their increased incorporation into the membrane and defective membrane formation. This membrane trafficking depends upon GTPases and lipid kinases, which are crucially dependent on

magnesium and are activated in magnesium excess. The change in membrane structure produced by alteration in glycoconjugates and cholesterol: phospholipid ratio can produce changes in the conformation of  $\text{Na}^+ - \text{K}^+$  ATPase resulting in further membrane  $\text{Na}^+ - \text{K}^+$  ATPase stimulation. The same changes can affect the structure of organelle membrane. This results in increased lysosomal stability. Altered peroxisomal membranes could lead to catalase hyperactivity noticed in hypodigoxinemic states. Thus there is increased membrane formation and increased stability of the membrane of cellular organelle in the left hemisphere dominant hypodigoxinemic state.

## References

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

