

Chapter 7

Archaeal Digoxin, Cerebral Dominance and
Lipid Metabolism

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 archaean digoxin (an endogenous membrane $\text{Na}^+\text{-K}^+$ ATPase inhibitor), dolichol (important in N-glycosylation of proteins), ubiquinone (component of 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 isoprenoidal metabolites and the rate limiting enzyme of the isoprenoid pathway - HMG CoA reductase in right hemispheric dominant and left hemispheric dominant individuals. The results are presented in this paper.

Results

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

(2) The results showed that the concentration of tryptophan was found to be higher in the plasma of left handed / right hemispheric dominant individuals while that of tyrosine, was lower. The results also showed that the concentration of tryptophan, was found to be lower in the plasma of right handed / left hemispheric dominant individuals while that of tyrosine was higher.

Discussion

Archaeal Digoxin Synthesis and Magnesium Status / Hemispheric Dominance

The 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 or 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 the 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 a 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 (bip/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}C -acetate into digoxin in the 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 suggests a downregulation of the isoprenoid pathway. There is a marked decrease in plasma digoxin levels consequent to its reduced synthesis in the 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 the 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 the 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 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. The intracellular negative calcium signal and positive magnesium signal can regulate diverse cellular processes. Serum magnesium was assessed in right handed / left hemispheric dominant individuals and was found to be increased.

There is increase in tryptophan and a reduction in tyrosine in the serum of left handed / right hemispheric dominant individuals. This could be due to the fact that digoxin can regulate neutral amino acid transport system with preferential promotion of tryptophan transport over tyrosine.

The results showed that the concentration of tryptophan, was found to be lower in the plasma of right handed / left hemispheric dominant individuals while that of tyrosine was higher. This could be due to the fact that digoxin can regulate neutral amino acid transport system with preferential promotion of tryptophan transport over tyrosine and because digoxin levels are low in right handed / left hemispheric dominant individuals.

Archaeal Digoxin - Golgi Body / Lysosomal Function - Hemispheric Dominance

The elevation in the level of dolichol in right hemispheric dominance individuals may suggest its increased availability for N-glycosylation of proteins. Magnesium deficiency can lead to defective metabolism of sphinganine producing its accumulation, which may lead to increased cerebroside and ganglioside synthesis. In magnesium deficiency the glycolysis, citric acid cycle and oxidative phosphorylation are blocked and more glucose-6-phosphate is channelled for the synthesis of glycosaminoglycans (GAG). Intracellular magnesium deficiency also results in defective ubiquitin dependent proteolytic processing of glycoconjugates as it requires magnesium for its function.

The decrease in the level of dolichol in right handed / left hemispheric dominant individuals may suggest its decreased availability for N-glycosylation of proteins. Magnesium excess can lead to increased catabolism of sphinganine leading to decreased cerebroside and ganglioside synthesis. In magnesium excess the glycolysis, citric acid cycle and oxidative phosphorylation are activated and less of glucose 6-phosphate is channelled for the synthesis of glycosaminoglycans (GAG). Intracellular magnesium excess also results in increased ubiquitin dependent proteolytic processing of glycoconjugates as it requires magnesium for its function.

Archaeal Digoxin, Cerebral Dominance and Mitochondrial Function

The concentration of ubiquinone decreased significantly in left handed / right hemispheric dominant individuals which may be the result of low tyrosine levels, reported in most of the disorders, consequent to digoxin's effect in preferentially promoting tryptophan transport over tyrosine. The aromatic ring portion of ubiquinone is derived from tyrosine. Ubiquinone, which is an important component of the mitochondrial electron transport chain, is a

membrane antioxidant and contributes to free radical scavenging. All this leads to defects in mitochondrial oxidative phosphorylation, incomplete reduction of oxygen and generation of the superoxide ion, which produces lipid peroxidation. There is also reduced scavenging of free radicals.

The concentration of ubiquinone increased significantly in right handed / left hemispheric dominant individuals which may be the result of increased tyrosine levels, consequent to digoxin deficiency promoting tyrosine transport over tryptophan. All this leads to improved efficiency in mitochondrial oxidative phosphorylation and reduced free radical generation. Ubiquinone excess also leads to increased free radical scavenging.

Cerebral dominance can thus play a crucial role in the regulation of the isoprenoid pathway and cell function.

References

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

