Chapter 8

Archaeal Digoxin, Cerebral Dominance and Golgi Body / Lysosomal Function

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 archaeal digoxin (an endogenous membrane Na^+-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 synthesis of an endogenous membrane Na^+-K^+ ATPase inhibitor, archaeal digoxin and changes in golgi body / lysosomal function 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 Na^+-K^+ ATPase activity and serum magnesium 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 Na^+-K^+ ATPase activity and serum magnesium were increased in right handed / left hemispheric dominant individuals.

(2) The results show an increase in the concentration of serum total GAG, glycolipids (ganglioside, glycosyl-diglyceride, cerebrosides and sulphatides) and carbohydrate components of glycoproteins (hexose, fucose and sialic acid) in left handed / right hemispheric dominant individuals. The increase in the carbohydrate components - total hexose, fucose and sialic acid - was not to the same extent in all cases suggesting qualitative change in glycoprotein structure. All the individual GAG fractions in the serum increased in left handed / right hemispheric dominant individuals. The activity of GAG degrading enzymes (beta glucuronidase, beta N-acetyl hexosaminidase, hyaluronidase and cathepsin-D) and that of glycohydrolases (beta galactosidase, beta fucosidase and beta glucosidase) showed significant increase in the serum in left handed / right hemispheric dominant individuals. The results show a decrease in the concentration of serum total GAG, glycolipids (ganglioside, glycosyl-diglyceride, cerebrosides and sulphatides) and carbohydrate components of glycoproteins (hexose, fucose and sialic acid) in right handed / left hemispheric dominant individuals. The decrease in the carbohydrate components - total hexose, fucose and sialic acid was not to the same extent in all cases suggesting qualitative change in glycoprotein structure. All the individual GAG fractions in the serum decreased in right handed / left hemispheric dominant individuals. The activity of GAG degrading enzymes (beta glucuronidase, beta N-acetyl hexosaminidase, hyaluronidase and cathepsin-D) and that of glycohydrolases (beta galactosidase, beta fucosidase and beta glucosidase) showed significant decrease in the serum in right handed / left hemispheric dominant individuals.

Discussion

Archaeal Digoxin Synthesis / Hemispheric Dominance

The recent reports on endogenous digoxin, a potent inhibitor of Na^{+}-K^{+} ATPase 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 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 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. 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 (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 HMQ 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 left hemispheric dominant state. 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 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.

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 on to detective metabolism of spinganine 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 channeled 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 results show an increase in the concentration of serum total GAG, individual GAG fractions, glycolipids and carbohydrate components of glycoproteins in left handed / right hemispheric dominant individuals. The increase in the carbohydrate components - total hexose, fucose and sialic acid - was not to the same extent in all cases, suggesting qualitative change in glycoprotein structure. The activity of GAG degrading enzymes (beta glucuronidase, beta N-acetyl hexosaminidase, hyaluronidase and cathepsin-D) and that of glycohydrolases (beta galactosidase, beta fucosidase and beta glucosidase) showed significant increase in the serum in right hemisphere dominant state. The increase in the activity of glycohydrolases and GAG degrading enzymes could be due to

reduced lysosomal stability and consequent leakage of lysosomal enzymes into the serum. The increase in the concentration of carbohydrate components of glycoproteins in spite of increased activity of many glycohydrolases may be due to their possible resistance to cleavage by glycohydrolases consequent to qualitative change in their structure. Proteoglycan complexes formed in the presence of altered calcium / magnesium ratios intracellularly may be structurally usually abnormal and resistant to lysosomal enzymes and may accumulate.

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). The results show a decrease in the concentration of serum total GAG, individual GAG fractions, glycolipids and carbohydrate components of glycoproteins in right handed / left hemispheric dominant individuals. The activity of GAG degrading enzymes (beta glucuronidase, beta N-acetyl hexosaminidase, hyaluronidase and cathepsin-D) and that of glycohydrolases (beta galactosidase, beta fucosidase and beta glucosidase) showed significant decrease in the serum in hypodigoxinemic left hemisphere dominant states, Intracellular magnesium excess also results in increased ubiquitin dependent proteolytic processing of glycoconjugates as it requires magnesium for its function. The decrease in the activity of glycohydrolases and GAG degrading enzymes could be due to increased lysosomal stability. Thus in the hypodigoxinemic left hemisphere dominant state there is increased lysosomal stability, increased ubiquitin dependent proteolytic processing of proteins and alteration in glycoconjugate metabolism leading to decrease in the

levels of glycolipids, the carbohydrate component of glycoproteins and glycosaminoglycans.

References

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