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Archaeal Digoxin Mediated Model for Gallstones

Gallstones are crystalline structures formed by concretion or accretion of normal or abnormal bile constituents. Cholesterol and mixed stones account for 80% of total stones. Mixed and cholesterol gallstones usually Contains more than 70% cholesterol monohydrate plus an admixture of calcium salts, bile acids and bile pigments, proteins, fatty acids, and phospholipids. There are several important mechanism in the formation of lithogenic bile. The most important is increased biliary secretion of cholesterol. This may occur in association with obesity and with increased activity of HMG CoA reductase the rate limiting enzymes of hepatic cholesterol synthesis. Lithogenic bile may also result from decreased hepatic secretion of bile salts and phospholipids, which may follow impaired hepatic synthesis. Patients with gallstones also tend to have reduced activity of hepatic cholesterol 7-alpha hydroxylase, the rate limiting enzyme for primary bile acid synthesis.

Thus an excess of biliary cholesterol in relation to bile acids and phospholipids may be due to hypersecretion of cholesterol, hyposecretion of bile acids, or both. While cholesterol saturation of bile is an important prerequisite for gallstone formation it is not sufficient by itself. An important abnormality is defective vesicle formation. Ordinary cholesterol and phospholipid are secreted into bile as unilamellar bilayered vesicles, which are unstable and are converted along with bile acids, into other lipid aggregates such as micelles. During micellation of vesicles, more phospholipid than cholesterol is transferred to mixed micelles, leading to unstable cholesterol-rich vesicles that aggregate into larger multilamellar vesicles from which cholesterol crystal aggregates.

A third important mechanism is nucleation of cholesterol monohydrate crystals which is greatly accelerated in human lithogenic bile; it is this feature rather than the degree of cholesterol supersaturation that distinguishes lithogenic from normal gallbladder bile. Accelerated nucleation of cholesterol

monohydrate in bile may be due to either an excess of pronucleating factors or a deficiency of antinucleating factors. Non-mucin and mucin glycoproteins and lysine phosphatidyl choline appear to be pronucleating factors, while apolipoproteins Al and All and other glycoproteins are antinucleating factors.

A fourth important mechanism in cholesterol gallstone formation concerns biliary sludge. The presence of biliary sludge implies two abnormalities (1) The normal balance between gall bladder mucin secretion and elimination has become deranged, (2) Nucleation of biliary solutes has occurred. Biliary sludge can develop with disorders that cause gall bladder hypomotility.

The isoprenoid pathway is an important metabolic pathway regulating cell metabolism. It produces three important components - cholesterol, dolichol and endosymbiotic archaeal digoxin. Cholesterol is an important component of gallstones. Dolichol is important in N-glycosylation and synthesis of mucoproteins. Mucoproteins are important pronucleating factors. Archaeal digoxin is an important endogenous regulator of neurotransmitter transport and can modulate gallbladder contractility. Therefore it was considered pertinent to study the isoprenoid pathway it patients presenting with gallstones.

Results

(1) The results showed that HMG C0A reductase activity, serum digoxin and dolichol were increased in patients with gallstones indicating upregulation of the isoprenoid pathway but serum ubiquinone, RBC sodium-potassium ATPase activity and serum magnesium were reduced.

(2) The results showed that the concentration of tryptophan, quinolinic acid, strychnine, nicotine and serotonin was found to be higher in the plasma of patients with gallstones while that of tyrosine, dopamine, morphine and norepinephrine was lower.

(3) The results show an increase in the concentration of serum carbohydrate components of glycoproteins (hexose, fucose and sialic acid) in patients with gallstones. The increase in the carbohydrate components - total hexose, fucose and sialic acid - in patients with gallstones was not to the same extent suggesting qualitative change in glycoprotein structure. The activity of glycohydrolases (beta galactosidase, beta fucosidase and beta glucosidase) showed significant increase in the serum of patients with gallstones.

(4) The cholesterol: phospholipid ratio of the RBC membrane was increased in patients with gallstones.

(5) The results showed that HMO CoA reductase activity serum digoxin and dolichol were increased and ubiquinone reduced in left handed / right hemispheric dominant individuals. The results also showed that HMG CoA reductase activity serum digoxin and dolichol were decreased and ubiquinone increased 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^{+}-K^{+} ATPase Inhibition in Relation to Gall Stones

The archaeaon steroidelle DXP pathway and the upregulated pentose phosphate pathway contribute to digoxin synthesis. The study shows an upregulated Isoprenoid pathway in gallstones with Increased HMG CoA reductase activity. Also the digoxin and dolichol levels were high and serum magnesium and RBC Na^{+}-K^{+} ATPase activity reduced. Digoxin has been demonstrated to be synthesized by the isoprenoid pathway.

The increase in endogenous digoxin, a potent inhibitor or membrane Na^{+}-K^{+} ATPase, can decrease this enzyme activity. In gallstones, 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 Ca^{++} via the voltage gated Calcium channel and increased release of Ca^{++} from intracellular endoplasmic reticulum Ca^{++} stores. This increase in intracellular Ca^{++} by displacing Mg^{++} from its binding sites, causes a decrease in the functional availability of Mg^{++}. This decrease in the availability of Mg^{++} can cause decreased mitochondrial ATP formation which along with low Mg^{++} can cause further inhibition of Na^{+}-K^{+} ATPase, since ATP-Mg^{++} 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 Mg^{++} 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 Mg^{++} and high intracellular Ca^{++} consequent to Na^{+}-K^{+} ATPase inhibition appear to be crucial to the pathophysiology of gallstones. Serum Mg^{++} was assessed in gallstones and was found to be reduced.

Magnesium can promote biliary secretion and in the presence of hypomagnesemia there is stagnation of biliary secretion.

Archaeal Digoxin and Regulation of Neurotransmitter Synthesis and Function in Relation to Gallstones

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 a reduction in tyrosine and its catabolites in the serum of patients with gallstones. 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 decrease in membrane Na^+-K^+ ATPase activity in patients with gallstones 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. This particular neurotransmitter pattern could contribute to gall bladder hypomotility. Biliary sludge can develop with disorders that cause gall bladder hypomotility.

Thus in the right hemisphere dominant hyperdigoxinemic state there is upregulated serotoninergic, cholinergic and glutamatergic transmission and downregulated dopaminergic, glycinergic and noradrenergic transmission. The same neurotransmitter pattern is seen in patients developing gallstones. Gallstones thus have a tendency to develop in right hemispheric dominant individuals.

Archaeal Digoxin and Regulation of Golgi Body / Lysosomal Function in Relation to Gallstones

The archaeaon glycosaminoglycoid and fructosoid contributes to glycoconjugate synthesis and catabolism by the process of fructolysis. The

elevation in the level of dolichol may suggest its increased availability of N-glycosylation of proteins. Intracellular Mg^{++} deficiency also results in defective ubiquitin dependent proteolytic processing of glycoconjugates as it requires Mg^{++} for its function. The increase in the activity of glycohydrolases 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. Altered mucoproteins can contribute to formation of gallstones. Non-mucin and mucin glycoproteins and lysine phosphatidyl choline appear to be pronucleating factors. Thus altered mucoproteins and glycoproteins of the bile can lead on to the formation of gallstones.

Archaeal Digoxin and Alteration in Membrane Structure and Membrane Formation in Relation to Gall Stones

The archaeaon steroidelle, glycosaminoglycoid and fructosoid contribute to cell membrane formation synthesizing cholesterol by the DXP pathway and glycosaminoglycans by fructolysis. There is increased cholesterol synthesis as noticed by increased HMG CoA reductase activity. This leads to cholesterol supersaturation of bile. Mg^{++} deficiency can inhibit phospholipid synthesis. Phospholipid degradation is increased owing to the increase in intracellular calcium activating phospholipase A_2 and D. Phospholipid secretion in the bile is thus reduced. Thus there is an excess of biliary cholesterol in relation to phospholipids. This leads to the formation of unstable cholesterol rich vesicles which aggregate to form large multilamellar vesicles from which cholesterol crystals aggregate. This could be the third important factor contributing to the formation of gallstones.

Archaeal Digoxin and Hemispheric Dominance in Relation to Gall Stones

The archaeaon related organelle - steroidelle, neurotransminoid and vitaminocyte contribute to hemispheric dominance. Thus the isoprenoid pathway upregulation and digoxin can contribute to the genesis of gallstones by three mechanisms. (1) Increased cholesterol and decreased phospholipid in the bile, (2) Altered biliary mucoproteins, and (3) Altered gall bladder motility. The upregulatory isoprenoid pathway and elevated digoxin is seen in right hemispheric dominant individuals. Thus right hemispheric dominance can lead on to the formation of gallstones. Hemispheric dominance has been associated with several systemic diseases.

References

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