4

Digoxin and the Bipolar Mood Disorder

Introduction

The isoprenoid pathway produces an endogenous membrane Na^+-K^+ ATPase inhibitor digoxin, a steroidal glycoside. Digoxin is reported to be secreted by the human hypothalamus. Previous reports have demonstrated alteration in the cation pump in bipolar mood disorder. Bipolar mood disorder and schizophrenia can occur in the same families suggesting that both these disorders are genetically interlinked. Digoxin is also reported to modulate neutral amino acid and neurotransmitter transport. Membrane Na^+-K^+ ATPase inhibition is reported to be lead to magnesium depletion and intracellular calcium excess. Therefore the following parameters were studied in bipolar mood disorder, major depressive disorder and schizophrenia-plasma HMG CoA reductase activity, serum digoxin, serum magnesium and RBC Na^+-K^+ ATPase activity. The levels of serum tyrosine, tryptophan and their catabolites were also assessed. These parameters were studied during the manic phase and depressive phase of the illness. It has been noticed that depression is strongly associated with left anterior frontal lesions. Right hemispheric lesions produce a manic syndrome. In infantile schizophrenia or autism right hemispheric dysfunction has been documented. The neurotransmitter patterns were compared with those in right handed / left hemisphere dominant and left handed / right hemisphere dominant individuals. The results are presented in this chapter.

Global warming can lead to osmotic stress consequent to dehydration. The increase in actinidic archaeal growth leads to cholesterol catabolism and digoxin synthesis. Digoxin produces membrane sodium potassium ATPase inhibition and increase in intracellular calcium producing mitochondrial dysfunction. This results in oxidative stress. The oxidative stress and osmotic stress can induce the enzyme aldose reductase which converts glucose to fructose. Fructose has got a low km value for ketokinase as compared to glucose. Therefore fructose gets

phosphorylated more to fructose phosphate and the cell is depleted of ATP. The cell depletion of ATP leads to oxidative stress and chronic inflammation consequent to induction of NFKB. Oxidative stress can open the mitochondrial PT pore producing release of cyto C and activation of the caspase cascade of cell death. The fructose phosphate can enter the pentose phosphate pathway synthesizing ribose and nucleic acid. The depletion of cellular ATP results in generation of AMP and ADP which are acted upon by deaminases causing hyperuricemia. Uric acid can produce endothelial dysfunction and vascular disease. Uric acid can also produce mitochondrial dysfunction. The fructose phosphate can enter the glucosamine pathway synthesizing GAG and producing mucopolysaccharide accumulation. Fructose can fructosylate proteins making them antigenic and producing an autoimmune response. This can lead to global warming related psychiatric disease.

Results

(1) The activity of HMG CoA reductase and the concentration of digoxin were decreased in the depressive phase of bipolar mood disorder, major depressive disorder and right handed / left hemispheric dominant individuals. The activity of erythrocyte membrane Na^+-K^+ ATPase and serum magnesium were increased in the depressive phase of bipolar mood disorder, major depressive disorder and right handed / left hemispheric dominant individuals. The activity of HMG CoA reductase and the concentration of digoxin were increased in the manic phase of bipolar mood disorder, schizophrenia and left handed / right hemispheric dominant individuals. The activity of erythrocyte membrane Na^+-K^+ ATPase and serum magnesium were decreased in the manic phase of bipolar mood disorder, schizophrenia and left handed / right hemispheric dominant individuals.

(2) The concentration of serum tryptophan, quinolinic acid and serotonin was decreased in the plasma of patients in depressive phase of bipolar mood disorder, major depressive disorder and right handed / left hemispheric dominant individuals while that of tyrosine, dopamine and noradrenaline was increased. The concentration of serum tryptophan, quinolinic acid and serotonin was increased in the plasma of patients in manic phase of bipolar mood disorder, schizophrenia and left handed / right hemispheric dominant individuals while that of tyrosine, dopamine and noradrenaline was increased.

(3) Nicotine and strychnine were not detected in the plasma of patients in the depressive phase of bipolar mood disorder; major depressive disorder and right handed / left hemispheric dominant individuals while morphine was detected in the plasma of these patients. Nicotine and strychnine were detected in the plasma of patients in the manic phase of bipolar mood disorder; schizophrenia and left handed / right hemispheric dominant individuals while morphine was not detected in the plasma of these patients.

Discussion

Archaeal Digoxin and Membrane Na^+-K^+ ATPase Inhibition in Relation to Mood Disorder

The archaeaon steroidelle DXP pathway and the upregulated pentose phosphate pathway contribute to digoxin synthesis. The decrease in the activity of HMG CoA reductase in the depressive phase of bipolar mood disorder major depressive disorder and right handed / left hemispheric dominant individuals suggests a downregulation of the isoprenoid pathway. There is a marked decrease in plasma digoxin and this decrease may be a consequence of decreased channelling of intermediates of the isoprenoid pathway for their biosynthesis. 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. The decrease in endogenous digoxin, a potent inhibitor of membrane Na^+-K^+ ATPase, can increase this enzyme activity. In the depressive phase of bipolar mood disorder, major depressive disorder and right handed / left hemispheric dominant individuals there was significant stimulation of RBC membrane Na^+-K^+ ATPase. The stimulation of Na^+-K^+ ATPase by digoxin is known 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 urn from intracellular endoplasmic reticulum calcium stores. This decrease in intracellular calcium by displacing magnesium from its binding sites causes an increase in the functional availability of magnesium. This increase in the availability of magnesium can increase mitochondrial ATP formation which along with increased magnesium can cause further stimulation 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 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 appear to be crucial to the pathophysiology of the depressive phase of bipolar mood disorder and major depressive disorder. The intracellular negative calcium signal and positive magnesium signal can regulate diverse cellular process. Serum magnesium was assessed in depressive phase of bipolar mood disorder, major depressive disorder and right handed / left hemispheric dominant individuals was found to be increased. Hypermagnesemia can lead on to depression. On the other hand the isoprenoid pathway and digoxin synthesis

was upregulated in the manic phase of bipolar mood disorder, schizophrenia and in left handed / right hemispheric dominant individuals leading on to membrane Na^+-K^+ ATPase inhibition and an increase in intracellular calcium and reduction in intracellular magnesium. The depressive phase of bipolar mood disorder and major depressive disorder is suggestive of hypodigoxinemia and left hemispheric chemical dominance and the manic phase of bipolar mood disorder and schizophrenia of right hemispheric chemical dominance and hyperdigoxinemia. Thus in bipolar mood disorder there is phasic variation in hypothalamic archaeal digoxin hypersecretion and fluctuating chemical hemispheric dominance. In major depressive disorderthere is permanent hypodigoxinemia and left hemispheric chemical dominance. In schizophrenia there is permanent hyperdigoxinemia and right hemispheric chemical dominance.

Archaeal Digoxin and Regulation of Neurotransmitter Synthesis and Function in Relation to Mood Disorder

The archaeaon neurotransminoid shikimic acid pathway contributes to tryptophan and tyrosine synthesis and catabolism generating neurotransmitters and neuroactive alkaloids. Digoxin, apart from affecting cation transport is also reported to influence the transport of various metabolites across cellular membranes, including amino acids and various neurotransmitters. Two of the amino acids in this respect are important, tryptophan, a precursor for strychnine and nicotine and tyrosine a precursor for morphine. We had already shown the presence of endogenous morphine in the brain of rats loaded with tyrosine and endogenous strychnine and nicotine in the brain of rats loaded with tryptophan. The results showed that the concentration of tryptophan, quinolinic acid and serotonin was found to be lower in the plasma of patients with depressive phase of bipolar mood disorder, major depressive disorder and right handed / left hemispheric dominant individuals while that of tyrosine, dopamine and

norepinephrine was higher. Serum of patients in depressive phase of bipolar mood disorder, major depressive disorder and right handed / left hemispheric dominant individuals showed the absence of strychnine and nicotine while morphine could be detected in the serum of these patients. Thus there is a decrease in tryptophan and its catabolites and increase in tyrosine and its catabolites in the serum of patients in the depressive phase of bipolar mood disorder, major depressive disorder and right handed / left hemispheric dominant individuals. This could be due to the fact digoxin can regulate neutral amino acid transport with preferential upregulation of tryptophan transport over tyrosine and that digoxin levels are low in depressive phase of bipolar mood disorder, major depressive disorder and right handed / left hemispheric dominant individuals. The increase in membrane Na^+-K^+ ATPase activity in depressive phase of bipolar mood disorder, major depressive disorder and right handed / left hemispheric dominant individuals 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 opposite is noticed in the manic phase of bipolar mood disorder, schizophrenia and left handed / right hemispheric dominant individuals with increase in the tryptophan catabolites - serotonin, quinolinic acid, strychnine and nicotine and a decrease in the tyrosine catabolites - dopamine, morphine and noradrenaline. This could be the result of elevated digoxin levels in left handed / right hemispheric dominant individuals, the manic phase of bipolar mood disorder and schizophrenia.

The low level of quinolinic acid, serotonin and strychnine in the depressive phase of bipolar mood disorder, major depressive disorder and in right handed / left hemispheric dominant individuals can contribute to reduced excitatory glutamatergic transmission as they are all positive modulators of the NMDA receptor. In the presence of hyperinagnesemia, 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 glutamate release into the synaptic junction and vesicular recycling. Decreased intracellular calcium in the post synaptic neuron can also inhibit the calcium dependent NMDA signal transduction. The plasma membrane glutamate transporter (on the surface of the glial cell and presynaptic neuron) is coupled to a 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. Reduced excitatory glutamatergic transmission, decrease serotoninergic transmission and upregulated morphinergic transmission can contribute to depression. Reduced glutamatergic transmission can contribute to the pseudodementia associated with depression.

In the manic phase of bipolar mood disorder, schizophrenia as well as in the left handed right hemispheric dominant individuals glutamatergic excitotoxicity could happen due to increased levels of positive modulators of the NMDA receptor - serotonin, quinolinic acid and strychnine. 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 increased neurotransmitter release into the synaptic junction and vesicular recycling. Increased intracellular calcium in the post synaptic neuron can also activate the calcium dependent NMDA signal transduction. The plasma membrane neurotransmitter transporter (on the surface of the glial 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 of Na^+-K^+ ATPase can promote glutamatergic transmission. Glutamatergic excitotoxic mechanisms have been described in the manic phase of bipolar mood disorder and schizophrenia. Strychnine displaces glycine from its binding sites and inhibits glycinergic inhibitory transmission in the brain. The glycine is free to bind to the strychnine insentive site of the NMDA receptor and promote excitatory NMDA transmission. Strychnine by blocking glycinergic transmission can contribute to the decreased inhibitory transmission in the manic phase of bipolar mood disorder and schizophrenia. In the manic phase of bipolar mood disorder and schizophrenia increased dopaminergic activity has been reported. Nicotine by interacting with nicotine receptors can facilitate the release of dopamine, promoting the dopaminergic transmission in the brain. This can explain the increased dopaminergic transmission in the presence of decreased dopamine levels. Low level of noradrenaline has also been related to manic phase of bipolar mood disorder and schizophrenia. The low levels of noradrenaline reported in our study agree with a defect in noradrenergic transmission reported previously in schizophrenia. Excess serotonin level documented in the serum of patients in the manic phase of bipolar mood disorder and schizophrenia is significant and is in agreement with the excess serotoninergic transmission reported in these conditions previously. The pattern of the neurotransmitters and neuroactive alkaloids in the manic phase of bipolar mood disorder and schizophrenia correlates with those obtained in left handed / right hemisphere dominant individuals.

Archaeal Digoxin and Fluctuating Hemispheric Dominance in Relation to Mood Disorder

The archaeaon related organelle-steroidelle, neurotransminoid and vitaminocyte contribute to hemispheric dominance. Thus the bipolar mood disorder represents phasic changes in digoxin secretion and fluctuating

hemispheric chemical dominance. There is a hyperdigoxinemic right hemisphere dominant manic phase and hypodigoxinemic left hemisphere dominant depressive phase. This alternating chemical hemispheric dominance represents phasic changes in digoxin secretion by the hypothalamus. In major depressive disorder there is permanent hypodigoxinemia and left hemispheric chemical dominance. We had previously reported elevated digoxin, tryptophan, serotonin, strychnine and nicotine in schizophrenia with reduced tyrosine, morphine, dopamine and noradrenaline levels. The pattern in schizophrenia correlates with those obtained in the manic phase of bipolar mood disorder and in left handed / right hemispheric dominant individuals. In schizophrenia there is permanent hyperdigoxinemia and right hemispheric chemical dominance. There are two way connections between the hypothalamus and the cerebral cortex. There are also projections from the hypothalamus to the serotoninergic dorsal raphe nucleus, noradrenergic, locus coeruleus, cholinergic nucleus basalis of meynert and dopaminergic nuclei in the brain stem. Thus phasic or permanent upregulation or downregulation of hypothalamic archaeal digoxin Secretion can modulate the function of these structures.

References

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