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# HYPOTHALAMIC DIGOXIN AND SCHIZOPHRENIA - A MODEL FOR CONSCIOUS AND SUBLIMINAL PERCEPTION AND ITS DYSFUNCTION IN SCHIZOPHRENIA

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## *ABSTRACT*

*In view of reports of an upregulated cation pump in genetically related Bipolar Affective Disorders the role of hypothalamic digoxin, an endogenous regulator of the cation pump was studied with special reference to its role as a modulator of glycoprotein synthesis. The study demonstrated elevated serum digoxin levels, elevated HMG CoA reductase activity suggesting increased digoxin synthesis, reduced sodium-potassium ATPase activity and altered sugar residues of serum glycoprotein in schizophrenia. A hypothalamic digoxin mediated model for conscious and subliminal perception is proposed and the significance of its dysfunction due to abnormal glycoprotein induced synaptic connectivity defects in schizophrenia is discussed.*

*Key words : Schizophrenia, digoxin, HMG CoA reductase, glycoproteins, conscious perception, subthreshold quantal perception.*

Studies have shown that there is an upregulation of the cation pump in Bipolar affective disorders (Cowen & Wood,1991). Bipolar affective disorder and schizophrenia have been shown to exist in the same families suggesting a common genetic basis for both diseases (Baron & Gruen, 1991). An endogenous sodium potassium ATPase inhibitor identified as the steroidal glycoside digoxin has been shown to be produced by the human hypothalamus (Haupert,1989). Digoxin being a steroidal glycoside is synthesised from the Isoprenoid pathway. Digoxin has also been shown to alter the sugar residues of glycoproteins and produce a protein processing defect in experimental animals (Kumudesa, 1988).

It was therefore considered pertinent to study serum digoxin level, RBC sodium potassium ATPase activity, HMG CoA reductase activity as a marker of digoxin synthesis and the sugar residues of serum glycoproteins in schizophrenia. The results are discussed in this paper. A hypothalamic digoxin mediated model for conscious and subliminal perception is proposed and the significance of its dysfunction in schizophrenia elucidated.

## MATERIAL AND METHOD

25 cases of schizophrenia diagnosed according to DSM-III-R criteria were chosen for the study. Freshly diagnosed cases before starting treatment were only included in the study. Patients with coexisting systemic disease like diabetes mellitus, systemic hypertension, renal and hepatic dysfunction were excluded from the study. Each patient had an age and sex matched control. Serum digoxin levels were estimated by radioimmunoassay (Andronico et al.,1992). RBC sodium potassium ATPase activity was measured by the method of Ishir (Ishir, 1993). HMG CoA reductase activity was assayed by

the method of Ramakrishnan (Ramakrishnan & Rao, 1975). For the estimation of the carbohydrate components of serum glycoprotein acetone dry defatted sera was subjected to papain digestion by the method of Wagh (Wagh, 1973). Total hexose was estimated by the method of Dubois (Dubois et al.,1956). Total fucose was estimated by the method of Dische and Shettles (Dische and Shettles,1951). Total sialic acid was estimated by the barbituric acid method of Warren (Warren et al.,1959). Total protein was estimated by the method of Lowry et al.(Lowry et al.,1952). Statistical analysis was done by students t-test.

## RESULT

Serum digoxin values were elevated in schizophrenic patients (120 ± 30 picograms/ml in schizophrenia versus not detectable in normal patients). There was a corresponding reduction in RBC sodium potassium ATPase activity. (1.249±0.08 mg $P_i$ liberated/mg protein in schizophrenia as against a control value of 3.75±0.98 - significantly different, $p< 0.01$). There was also increased HMG CoA reductase activity in schizophrenia as compared to normal population. (HMG CoA/mevalonate ratio was 0.725 ± 0.07 in schizophrenia as against a control value of 1.058 ± 0.03 significantly different, $p<0.01$. Lower the ratio higher the enzyme activity). Concentration of total hexose (49.12±1.08 mg/gm protein of dry defatted tissue as against a control value of 60.55±1.86 significantly different, $p<0.01$), fucose (5.39±0.21 mg/gm protein of dry defatted tissue as against a control value of 7.82±0.26 significantly different, $p<0.01$) and sialic acid (3.51±0.10 mg/gm protein of dry defatted tissue as against a control value of 4.83±0.12 significantly different, $p<0.01$) in the serum glycoproteins showed a significant decrease.

## DISCUSSION

The increase in the concentration of digoxin in patients of schizophrenia is an important observation. Digoxin is a potent inhibitor of sodium potassium ATPase and the decrease in the activity of this enzyme observed in schizophrenia is due to increased levels of digoxin. It is known that endogenous digoxin synthesis is by the isoprenoid pathway. The increase in the functioning of the isoprenoid pathway as evidenced by increased activity of HMG CoA reductase. (which catalyses the rate limiting step of this pathway) may suggest increased endogenous digoxin synthesis. Digoxin promotes dopamine release in the mammalian brain (Arbuthnott et al.,1990). This could account for the hyperdopaminergic transmission in the mesolimbic system producing the psychotic symptoms of schizophrenia (Andreasen,1992). There is an underlying generalised disorder of consciousness or self awareness that impairs the ability to think with metarepresentations in schizophrenia (Andreasen,1992). PET studies have show activation of the thalamus and the cingulate cortex in disorders of self monitoring and mentalising associated with schizophrenia (Andreasen,1992). The evidence of increased hypothalamic digoxin points to a role for the hypothalamus. The hypothalamus is connected to the thalamus by the mamillothalamic tract. There are two way connections between the cingulate cortex and the anterior thalamic nucleus. There are also two way connections between the anterior cingulate and hypothalamus. The hypothalamus - anterior thalamus - anterior cingulate circuit would play a role in mediating conscious perception and disorganised synaptic connectivity in this circuit could lead to schizophrenia. It is known that inhibition of sodium potassium ATPase by digoxin leads to intracellular magnesium depletion (Haga,1992). Magnesium is required for the formation of dolichol-1-phosphate required for N-glycosylation and for the synthesis of nucleoside diphosphate sugars required for O-glycosylation. The intracellular deficiency of magnesium may lead to defective glycosylation of proteins. The decrease in the concentration of carbohydrate moieties of serum glycoprotein

in schizophrenia may be due to the effect of digoxin as reported before (Kumudesan, 1988). Changes in brain glycoproteins can produce altered synaptic connectivity and the cortical cytoarchitectural disorganization of the temporolimbic cortex reported in schizophrenia (Jakob & Beckmann, 1986).

The right hemispheric cingulate cortex contains a map of emotional relevance of the external world with a corresponding topographically organised maps of the external world in the anterior thalamic nucleus and the reticular nucleus of the thalamus (Kinney & Samuels,1994). The short term changing map of external world is probably coded by fast glutamatergic synapses and a long term map of external world coded for in glutamatergic peptidergic synapses. Perceptual binding important in consciousness occurs when all the neurons associated with any one object's perceptual map in layer 5 cingulate cortex fire in bursts and in a synchronised pattern but out of synchrony with those representing other objects (Crick,1994). When a particular object is perceived, the heteromodal sensory association cortex area 39, 40 - cingulate connections activate the short term and long term cingulate maps of external world and serves to update the maps with the new perceived sensory information. When an object is perceived there is a simultaneous activation of the anterior cingulate-hypothalamic 2 way connections and liberation of learned fixed quanta of digoxin from the hypothalamus to stimulate the short term and long term maps of the external world in the cingulate cortex and their resultant synchronised burst firing. Fixed quanta of digoxin by its sodium potassium ATPase inhibition can produce a paroxysmal depolarisation shift resulting in sustained synchronised burst firing of cingulate cortical neurons. During this process the short term changing glutamatergic maps of external world gets compared with the long term peptidergic schema of experience and a choice is made. This produces an awareness of external world in relation to previous experience. The human self thus exists as a collection of perceived sensory impression of the external world and is momentary and it is the comparison between the long term and short term maps that gives a sense of continuity to the momentary human self. The two way hypothalamo-cingulate connections helps to construct and code for the long term anterior cingulate peptidergic perceptual map in cingulate cortical synapses based on data from the changing short term glutamatergic cingulate maps. This is by the effect of digoxin on glutamatergic peptide efflux from the presynaptic cingulate cortical neurons by way of its reported binding to P glycoprotein a cellular efflux pump in the presynaptic neuron (Tanigawara,1992).

The hypothalamic-anterior thalamic-anterior cingulate pathway mediates focussed attention important in consciousness (Crick,1994). All axons that pass either way between the cingulate cortex and anterior thalamic nucleus must go through the thalamic reticular nucleus and all give off collateral excitatory glutamatergic branches that innervate the reticular nucleus. The reticular nucleus in turn provides an inhibitory GABAergic innervation back to the anterior thalamic nucleus that provides the input (Crick,1994). Reticular nucleus is involved in mediating selective attention by intensifying or detaching a particular active thalamic input into the cortex. The amplification or focussing and detachment of attention occurs by digoxin's effect in promoting GABAergic and glutamatergic transmission by inhibiting the glial uptake of the neurotransmitter and increasing its synaptic content (Sakai et al., 1990; Hisaka et al.,1990). The back projections from the short term cingulate map of external world to hypothalamus decides whether hypothalamic digoxin should act on glutamatergic or GABAergic connections and thus focus or detach attention.

Short term memory or working memory important in conscious perception depends on the hypothalamic - anterior thalamic - anterior cingulate reverberatory circuit as well as the phenomena of sustained synchronised burst firing of neurons in layer 5 of the cingulate cortex

(Crick,1994). Sustained synchronised burst firing can temporarily strengthen the relevant synapses so that this particular pattern of firing is recalled quickly - atype of short term memory - working memory. Transient synaptic changes of this type is due to alteration in the presynaptic neuronal calcium (Crick,1994). Digoxin has been reported to alter Sodium-Calcium exchange and increase the intraneuronal calcium concentration (Kramer et al.,1991). The digoxin induced sodium potassium ATPase inhibition leads also to a paroxysmal depolarisation shift resulting in sustained synchronised burst firing of cingulate neuronal net work. The anterior thalamic-anterior cingulate reverberatory circuit mediating short term memory - working memory is glutamatergic. Digoxin could amplify the circuit by its inhibitory effect on the glial uptake of glutamate and increasing the synaptic glutamate content leading to upregulation of glutamatergic transmission (Crick,1994; Hisaka,1990).

The perceived element in quantal or subliminal perception which could play a role in schizophrenic symptomatology could be the quanta of light, sound, vibration pressure and matter dependent electric and magnetic fields. The brain functions as a quantum computer with the quantum computer memory elements constituted of superconducting quantum interference devices - the SQUIDS which can exist as superpositions of macroscopic states (Lockwood,1989). Bose condensation, the basis of superconductivity is achievable at room temperature in the Frohlich model in biological systems. The dielectric protein molecules and polar sphingolipids of the neuronal membrane, nucleosomes which are combination of basic histones and nucleic acid and cytoplasmic magnetite molecules are excellent electric dipole oscillators which exist under a steep neuronal membrane voltage gradient. The individual oscillators are energised with a constant source of pumping energy from outside, by digoxin binding to membrane sodium potassium ATPase and producing a paroxysmal depolarisation shift in the neuronal membrane. This prevents the dipole oscillators from ever settling into thermal equilibrium with the cytoplasm and interstitial fluid which is always kept at constant temperature (Lockwood,1989). There are connections between the hypothalamus and cerebral cortex and digoxin may serve as a neurotransmitter for these synapses. Bose condensed states produced by digoxin mediated dielectric protein molecular pumped phonon system could be used to store information which might be encoded - all within the lowest collective frequency mode - by appropriately adjusting the amplitudes of and phase relations between the dipole oscillators. The external world sensory impressions exist in the cortical dipole oscillators as probabilistic multiple superimposed patterns-the U phase of quantum mechanics. The part of incoming quantal data maps of the external world built by subliminal perception in logical sequence and corollary to the cingulate external world maps built by conscious perception is chosen. Hypothalamo-cingulate connections mediated by digoxin acting on the neuronal membrane help to magnify the chosen map to 1 graviton criteria and to the threshold required for the neuronal network to fire and consciousness. It is then integrated into the cingulate conscious perceptual external world map. The comparison occurs by quantal non-local quasicrystal tiling effect which mediate the activation and deactivation of synapses through the contraction and growth of dendritic spines (Lockwood,1989). This model of quantal perception gives a mechanism for extrasensory or subliminal perception. Hallucination could be due to subliminal extrasensory perception. Paranoid delusions of persecution and alien control could be due to subliminal perception of thoughts of other persons. Normally quantal subliminal perception plays a minor role being a primitive form of perception and is subservient to conscious perception. Hypothalamic digoxin induced altered synaptic glycoproteins can lead to synaptic connectivity defects in the hypothalamo -anterior thalamic-cingulate circuit mediating conscious perception and disrupt conscious perceptive mechanism in schizophrenia. But increased hypothalamic digoxin secretion also leads to a hyperfunctional digoxin mediated dielectric protein pumped phonon system and hypersensitive subliminal quantal perception

which is also defectively integrated into conscious perception and is not regulated by conscious perception in schizophrenia. The R part of quantal subthreshold perception is not deterministic and it introduces a completely random element into the time evolution and in the operation of R there might be a role for free will, an important component of conscious perception.

It is consciousness that converts the world of probabilities into the classical objective real world of matter by the act of making an observation. This process is deranged if the observer or human consciousness is dysfunctional owing to a disordered hypothalamo-anterior thalamic-cingulate circuit. This would lead to defective perception of the external world and delusions such as seeing a rope as a snake. ECT produces loss of consciousness and benefit in schizophrenia by interfering with the system of biological dipole oscillator.

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