Chapter 9

Neurology of Sleep

Introduction

The hypothalamus is involved in the control of REM sleep and NREM sleep. This suggests a possible role for archaeal digoxin; an endogenous membrane Na^+-K^+ ATPase inhibitor. The control of NREM sleep appears to involve a complex series of interactions among widely located brain structures rather than the action of a single center. For example, wakefulness may be promoted by cells in the posterior hypothalamus and NREM sleep, by activity in specific regions of the basal forebrain, the brain stem and the thalamus. The thalamo-cortical connections are important in sleep spindle generation. Transection experiments in animals demonstrated that pontomedullary structures particularly in the region of the locus coeruleus, are crucially involved in the production of REM sleep phenomena. Cholinergic stimulation of this region may induce REM sleep and cells in this region are particularly active during stage REM sleep. Nevertheless, interactions with other cerebral structures, such as the hypothalamus, influence the control of REM sleep. The descending inhibitory pathway from the region of the locus coeruleus leading to the production of REM atonia probably involves the lateral tegmentoreticular tract, projections to the nucleus magnocellularis and then to the ventrolateral reticulospinal tract leading to postsynaptic inhibition of the alpha motor neuron. Ascending projections from the pons to the lateral geniculate body and on to the cortex are involved in the expression of pontogeniculo-occipital waves, which are seen during wakefulness and REM sleep and may be related to phasic REM events such as REMs and muscle twitches. Projections to the thalamus may mediate the desynchronization of cortical activity seen during REM sleep.

It was considered pertinent to study the neurotransmitter patterns in patients presenting with chronic insomnia diagnosed according to the DSM-IV criteria. The hypothalamus produces an endogenous membrane Na^+-K^+ ATPase

inhibitor called digoxin. Endogenous digoxin is a steroidal glycoside and has demonstrated to be synthesized by the isoprenoid pathway. Digoxin can regulate multiple neurotransmitter systems. Therefore hypothalamic archaeal digoxin may possibly regulate sleep patterns. The isoprenoid pathway related cascade and digoxin synthesis was studied in chronic insomnia. Since digoxin can regulate multiple neurotransmitter systems it could possibly play a role in the genesis of cerebral dominance. Digoxin synthesis and neurotransmitter patterns were also assessed in individuals of differing cerebral dominance in order to study the role of cerebral dominance in regulating sleep patterns. The results are presented in this paper.

Results

(1) The results showed that individuals with normal sleep patterns had decreased HMG CoA reductase activity and serum digoxin as well as increased RBC Na^+-K^+ ATPase activity and serum magnesium levels. The results showed that patients with chronic insomnia had increased HMG CoA reductase activity and serum digoxin levels with reduced RBC membrane RBC Na^+-K^+ ATPase activity and serum magnesium levels.

(2) The results showed that individuals with normal sleep patterns had increased levels of tyrosine and its catabolites (dopamine, noradrenaline and morphine) and reduced levels of tryptophan and its catabolites (serotonin, quinolinic acid, strychnine and nicotine). The results showed that patients with chronic insonmia had decreased levels of tyrosine and its catabolites (dopamine, noradrenaline and morphine) and increased levels of tryptophan and its catabolites (serotonin, quinolinic acid, strychnine and nicotine).

(3) Serum digoxin levels were increased and RBC Na^+-K^+ ATPase activity was reduced in right hemispheric dominant individuals. Serum digoxin

levels were reduced and RBC Na^+-K^+ ATPase increased in left hemispheric dominant individuals. The bihemispheric dominant individuals had intermediate values. The levels of tryptophan, serotonin, quinolinic acid, nicotine and strychnine were elevated and that of tyrosine, dopamine, noradrenaline and morphine decreased in right hemispheric dominant individuals. The levels of tryptophan, serotonin, quinolinic acid, nicotine and strychnine were decreased and that of tyrosine, dopamine, noradrenaline and morphine Increased in left hemispheric dominant individuals.

Discussion

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

The archaeaon steroidelle DXP pathway and the upregulated pentose phosphate pathway contribute to digoxin synthesis. The results showed that people with normal sleep patterns had decreased digoxin synthesis and increased membrane Na^+-K^+ ATPase activity with increased serum magnesium levels. Membrane Na^+-K^+ ATPase stimulation leads to a decrease in intracellular calcium and an increase in intracellular magnesium. Hypermagnesemia tends to produce somnolence. The low levels of digoxin could be due to its reduced synthesis. Studies from our laboratory have demonstrated the synthesis of endogenous digoxin, a steroidal glycoside by the isoprenoid pathway. Low level of digoxin can stimulate membrane Na^+-K^+ ATPase activity. The low level of digoxin is responsible for the increased neuronal tyrosine load and reduced neuronal tryptophan load in these groups of chronic insomnia patients. Digoxin promotes neutral amino acid tryptophan transport over tyrosine. Individuals with normal sleep patterns also had elevated levels of tyrosine catabolites (dopamine, noradrenaline and morphine).

The results showed that people with chronic insomnia had increased digoxin synthesis and decreased membrane Na^{+}-K^{+} ATPase activity with decreased serum magnesium levels. Membrane Na^{+}-K^{+} ATPase inhibition leads to an increase in intracellular calcium and a decrease in intracellular magnesium. Hypomagnesemia lends to produce irritability and CNS stimulation leading to chronic insomnia. The increased levels of digoxin could be due to its increased synthesis. Increased levels of digoxin can inhibit membrane Na^{+}-K^{+} ATPase activity. The increased level of digoxin is responsible for the decreased neuronal tyrosine load and increased neuronal tryptophan load in these groups of patients. Digoxin promotes tryptophan transport over tyrosine. They also had decreased levels of tyrosine catabolites (dopamine, noradrenaline and morphine). There is reduced synthesis of endogenous morphine from tyrosine. Reduced morphinergic transmission is associated with chronic insomnia. The synthesis of serotonin, nicotine and strychnine from tryptophan is increased. Increased level of strychnine blocks the glycinergic inhibitory transmission in the brain leading to CNS stimulation and chronic insomnia. Nicotine is a CNS stimulant and promotes cholinergic transmission in the brain leading on to chronic insomnia. In the presence of hypomagnesmia, the Mg^{++} block on the NMDA receptor is removed leading to NMDA excitotoxicty. The increased presynaptic neuronal Ca^{++} can produce cyclic AMP dependent phosphorylation of synapsins resulting in increased neurotransmitter release into the synaptic junction and vesicular recycling. Increased intracellular Ca^{++} in the post synaptic neuron can also activate the Ca^{++} dependent NMDA signal transduction. The plasma membrane neurotransmitter transporter (on the surface of the glial cell and presynaptic neuron) is coupled to a Na^{+} 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, inhibitory Na^{+}-K^{+} ATPase can promote glutamatergic

transmission. The elevated levels of quinolinic acid, strychnine and serotonin can also contribute to NMDA excitotoxicity. Quinolinic acid, strychnine and serotonin are also positive modulators of the NMDA receptor. Strychnine displaces glycine from its binding sites and inhibits glycinergic inhibitory transmission in the brain. The glycine is free to bind to the strychnine insensitive site of the NMDA receptor and promote excitatory NMDA transmission. Increased glutamatergic transmission can lead to CNS stimulation and chronic insomnia.

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

The archaeaon neurotransminoid shikimic acid pathway contributes to tryptophan and tyrosine synthesis and catabolism generating neurotransmitters and neuroactive alkaloids. Previous studies have demonstrated synthesis of endogenous morphine from tyrosine. Morphine is concerned with sleep behaviour. Endogenous opioid peptides tend to produce somnolence. The reduced synthesis of serotonin, strychnine and nicotine is also significant. Studies from our laboratory have demonstrated the synthesis of endogenous strychnine and nicotine from tryptophan. Strychnine blocks the glycinergic inhibitory transmission in the brain. Increased glycinergic inhibitory transmission consequent to decreased strychnine tends to produce normal sleep patterns. This has not been reported before. Also, there is a decreased synthesis of nicotine which promoted cholinergic transmission. Reduced cholinergic transmission could also be associated with normal sleep patterns. Nicotine and strychnine are both CNS stimulants. Reduced synthesis of nicotine from tryptophan tends to produce normal sleep patterns. In the presence of hypermagnesmia, the Mg^{++} block on the NMDA receptor is removed leading to reduced NMDA transmission. The decreased presynaptic neuronal Ca^{++} can produce decreased cyclic AMP dependent phosphorylation of synapsins

resulting in decreased neurotransmitter release into the synaptic junction and vesicular recycling. Decreased intracellular Ca^{++} in the post synaptic neuron can also inhibit the Ca^{++} dependent NMDA signal transduction. The plasma membrane neurotransmitter transporter (on the surface of the glial cell and presynaptic neuron) is coupled to a Na^{+} gradient which is stimulated by the activation 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 membrane Na^{+}-K^{+} ATPase can inhibit glutamatergic transmission.

The low levels of quinolinic acid, strychnine and serotonin can also contribute to reduced NMDA transmission. Quinolinic acid, strychnine and serotonin are also positive modulators of the NMDA receptor. Strychnine displaces glycine from its binding sites and inhibits glycinergic inhibitory transmission in the brain. The glycine is free to bind to the strychinine insensitive site of the NMDA receptor and promote excitatory NMDA transmission. Glutamate is the principle excitatory neurotransmitter in the brain. Decreased glutamatergic transmission can lead to CNS inhibition and normal sleep patterns.

Archaeal Digoxin and Hemispheric Dominance in Relation to Sleep

The archaeaon related organelle-steroidelle, neurotransminoid and vitaminocyte contribute to hemispheric dominance. The neurotransmitter patterns of elevated dopamine, morphine and noradrenaline, and reduced serotonin, strychnine and nicotine is associated with left hemispheric dominance. Left hemispheric dominant individuals may have an increased predilection for normal sleep patterns. The neurotransmitter patterns of reduced dopamine, morphine and noradrenaline and increased serotonin, strychnine and nicotine is associated with right hemispheric dominance. Right hemispheric dominant individuals may have an increased predilection for chronic insomnia.

References

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