Chapter 8

Archaeal Digoxin Mediated Model for Addiction

Introduction

Endosymbiotic archaeal metabolonomics can be related to addiction. Addiction has been classified as an endogenous morphine deficiency syndrome. Morphine has been demonstrated to be synthesized from the amino acid tyrosine in the human brain. Endogenous morphine may play a crucial role in modulating mesolimbic-mesocortical dopaminergic sensitisation. The mesolimbic-mesocortical dopaminergic (DA) system is crucial in the understanding of substance abuse. All drugs of dependence share a common feature of mesolimbic DA stimulation. Ventral tegmental dopaminergic (VTA DA) neurons project to nucleus accumbens (NAS), anterior cingulate cortex and prefrontal cortex. The reinforcing and addicting potential of all substance of abuse including morphine appear to require mesolimbic DA activation which is modulated by GABA inhibiting signal. VTA DA neurons are regulated by inhibiting GABAergic outflow from ventral pallidum. Activation of GABA receptors expressed on VTA DA neurons results in inhibition of dopaminergic activity through hyperpolarisation of DA synaptic potential. There are also important VTA DA synaptic inputs mediated by excitatory amino acids (EAA). NMDA receptor activation stimulates burst firing which promotes additional DA release in the NAS. The issue of depolarisation inactivation of DA neurons related to EAA stimulation is also important. In DA neurons in a state of excessive EAA induced depolarisation inactivation, the normally inhibitory effect of GABA_B hyperpolarisation may result in DA excitation. It is also known that mu opioid agonists can excite VTA DA neurons by hyperpolarisation of local interneurons. Just as stimulation of presynaptic GABA_A receptors on GABA inhibitory neurons can disinhibit DA neurons in the VTA so can stimulation of mu receptors lying on GABA interneurons.

Four sets of neurotransmitters are thus important in addiction - dopamine, morphine, glutamate, inhibitory GABA and serotonin. The hypothalamus produces a steroidal glycoside digoxin which can modulate multiple neurotransmitter systems. The hypothalamic archaeal steroidal glycoside digoxin can regulate neutral amino acid transport with preferential upregulation of tryptophan transport over tyrosine. There for it was considered pertinent to study digoxin status as well as level of tryptophan catabolites (serotonin, quinolinic acid, strychnine and nicotine) and tyrosine catabolites (dopamine, morphine and noradrenaline) in addictive individuals. It was also considered pertinent to compare the neurotransmitter patterns in right handed / left hemispheric dominant and left handed / right hemispheric dominant individuals versus addictive individuals to see if hemispheric dominance may play a role in addiction.

Results

- (1) The activity of HMG CoA reductase and the concentration of digoxin were increased in addictive individuals and left handed / right hemispheric dominant individuals. The activity of erythrocyte membrane Na⁺-K⁺ ATPase and serum magnesium were decreased in addictive and left handed / right hemispheric dominant individuals.
- (2) The concentration of serum tryptophan, quinolinc acid and serotonin was increased in the plasma of addicitive patients and left handed / right hemispheric dominant individuals while that of tyrosine, dopamine and noradrenaline was decreased.
- (3) Nicotine and strychnine were detected in the plasma of patients with addiction and left handed / right hemispheric dominant individuals but were not detectable in control serum, Morphine was not detected in the plasma of addictive individuals and left handed / right hemispheric dominant individuals while it was present in the control serum.



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Discussion

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

The archaeaon steroidelle DXP pathway and the upregulated pentose phosphate pathway contribute to digoxin synthesis. The increase in endogenous digoxin, a potent inhibitor of membrane Na⁺-K⁺ ATPase in addictive individuals can decrease this enzyme activity. There is increased digoxin synthesis as evidenced by elevated HMG CoA reductase activity. HMG CoA reductase is the rate limiting enzymes of the isoprenoid pathway. Studies in our laboratory have shown that digoxin is synthesized by the isoprenoid pathway. 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 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 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 Na⁺-K⁺ ATPase activity first triggered by digoxin. Low intracellular magnesium and high intracellular calcium consequent to Na⁺-K⁺ ATPase inhibition appear to be crucial to the pathophysiology of addiction. Serum magnesium was assessed in addiction and was found to be reduced.

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

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 addictive individuals. This could be due to the fact that digoxin can regulate the neutral amino acid transport system with a preferential promotion of tryptophan transport over tyrosine. The low level of dopamine consequent to its reduced synthesis owing to decreased tyrosine levels is significant. Low levels of dopamine in addicts can lead on to inhibition of the mesolimbic-mesocortical dopaminergic system and substance abuse. The low tyrosine levels noted in these patients leads to reduced synthesis of morphine. Morphine activates the mesolimbic-mesocortical DA system. It is known that mu opioid agonist can excite VTA DA neurons by hyperpolarisation of local interneurons. In morphine deficiency there is inhibition of mesolimbic-mesocortical dopaminergic system. It should also be noted that there is a hypothesis that might link alcohol addiction to this system as well. Alcohol may induce alteration of the chemical disposition of dopamine. In certain tissues such as the brain and its mesolimbic-mesocortical DA system, there is a relatively low aldehyde-oxidizing ability. In such a context, alcohol biotransformation to its active metabolite, acetaldehyde, blocks the normal conversion of amine derived aldehyde to its corresponding acid, due to inhibition of aldehyde dehydrogenase. The intermediate aldehyde that accumulates is highly reactive and may condense with the parent amine present. In the case of DA and its aldehyde, which is 3,4-dihydroxyphenyl acetaldehyde, the condensation compound is tetrahydropapaveroline (norlaudanosoline). Norlaudanosoline may go on after several steps to form morphine-like alkaloids with addictive potential and



morphine itself. In such a cascade, it is hypothesized that alcohol could lead to endogenous production of morphine and morphine-like compounds to counteract the endogenous morphine deficiency.

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 presynaptie 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 Na⁺-K⁺ ATPase can promote glutamatergic transmission. The elevated levels of quinolinic acid, strychnine and serotonin can also contribute to NMDA excitotoxicity. 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. Quinolinic acid and serotonin are also positive modulators of the NMDA receptor. Increased glutamatergic transmission resulting in excitotoxicity has been implicated in addiction. Excitatory amino acids can promote the release of dopamine in the nucleus accumbens. But there is also depolarisation inactivation of DA neurons with excessive EAA stimulation. This results in inactivation of the mesolimbicmesocortical dopaminergic system.

The same mechanism hold good in the case of excess nicotine synthesis from tryptophan noticed in these cases. We have demonstrated the synthesis of nicotine from tryptophan in the brain of rats loaded with tryptophan. Nicotine can also produce a biphasic effect on mesolimbic-mesocortical dopaminergic neurons with initial activation followed by depolarisation inactivation of DA neurons. High levels of nicotine can produce permanent depolarisation inactivation of DA neurons of the mesolimbic-mesocortical dopamine system leading on to addiction.

The increased synthesis of strychnine from tryptophan demonstrated in these cases is also significant. We have demonstrated the synthesis of strychnine from tryptophan in the brain of rats loaded with tryptophan. Strychnine can block the glycinergic inhibitory transmission in the brain. This glycine is free to modulate NMDA transmission acting at the strychnine Sensitive site of the NMDA receptor and promote glutamatergic excitotoxicity. Activation of inhibitory GABA receptors expressed on VTA DA neurons results in inhibition of dopaminergic activity. The strychnine induced glutamatergic excitotoxicity and reduced inhibitory glycine/GABA transmission can inhibit dopaminergic activity in the mesolimbic-mesocortical dopaminergic system leading on substance abuse and addiction.

The increased serotonin levels noted in addictive individuals is also significant. The acute drug state has been related to increased serotoninergic activity. Increased serotonin and quinolinic acid being positive modulators of the NMDA receptor promotes NMDA excitotoxicity leading on to depolarisation inactivation of mesolimbic-mesocortical dopaminergic neurons.

Archaeal Digoxin and Hemispheric Dominance in Relation to Addiction

The archaeaon related organelle-steroidelle, neurotransminoid and vitaminocyte contribute to hemispheric dominance. The neurotransmitter pattern in left handed / right hemisphere dominant individual correlated with the neurotransmitter pattern in addiction. Thus in the right hemisphere dominant



hyperdigoxinemic state there is upregulated serotoninergic, nicotinergic, strychninergic and glutamatergic transmission and downregulated dopaminergic, morphinergic and noradrenergic transmission. This particular neurotransmitter pattern can lead on to substance abuse and addiction.

References

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

