Chapter 6

Archaeal Nicotine - Description of the Hypo - and Hyper-Nicotinergic State in Relation to Neuropsychiatric Diseases

Introduction

Endogenous morphine has been reported to be synthesized in the mammalian brain. Morphine can be synthesized from intravenously injected salutaridine, thebaine and codeine, and thebaine can be converted to morphine when incubated with microsomal preparation from the liver, kidney and brain of rats.

The pyridine ring of nicotine is derived biosynthetically from nicotinic acid, which is derived from tryptophan. The pyrrolidine ring is derived from ornithine. Like acetylcholine, nicotine initially stimulates the autonomic ganglia, adrenal medulla and myoneural junction by rapidly depolarising the cell bodies, but in large doses it produces persistent depolarisation and a blockade or paralysis of these structures. Newhouse et al. suggested involvement of nicotine receptors in neurodegenerative disorders such as Alzheimer's disease (AD) and Parkinson's disease (PD) in which loss of nicotinic receptors has been described.

In this context it was considered pertinent to look for endogenous nicotine in neuropsychiatric disorders. The disorders studied include: manic depressive psychosis, schizophrenia, primary generalised epilepsy, Parkinson's disease, multiple sclerosis and CNS glioma. The serum levels of tyrosine and tryptophan were also estimated.

Results

No nicotine could be detected in the serum of control subjects. Patients with epilepsy, PD and MDP contained trace amounts of nicotine (1.25, 1.07 and 1.01 μg/100 ml serum respectively). On the other hand, the serum of patients with schizophrenia, CNS glioma and syndrome X with multiple lacunar state contained higher amounts of nicotine (5.287, 4.56 and 9.72 μg/dl respectively).

Serum tryptophan was found to be elevated in primary generalised epilepsy, Parkinson's disease, multiple sclerosis, CNS glioma, schizophrenia, MDP, syndrome X with multiple lacunar state. Serum tyrosine levels were found to be decreased in primary generalised epilepsy, Parkinson's disease, schizophrenia, CNS glioma, syndrome X multiple lacunar state. Dopamine levels were also found to be low in multiple sclerosis, CNS glioma, syndrome X with multiple lacunar state, Primary generalised epilepsy, Parkinson's disease and schizophrenia.

RBC Na^+-K^+ ATPase was found to be reduced in primary generalised epilepsy, Parkinson's disease, multiple sclerosis, CNS glioma, schizophrenia and syndrome X with multiple lacunar state but was normal in MDP.

Discussion

The increase in serum tryptophan and decrease in tyrosine in the serum of patients of many of these disorders is a significant observation in the light of altered levels of the alkaloids. It is known that tryptophan is the precursor for nicotine. The presence of nicotine in the serum of patients of most disorders studied may be a reflection of their synthesis from tryptophan. The absence of nicotine in MS in spite of an increase in the tryptophan level may be a reflection of some block in their synthesis in spite of increased availability of tryptophan.

The inhibition of membrane Na^+-K^+ ATPase activity in most the disorders studied is another significant observation. This inhibition can result from increased depolarising nicotinergic transmission. It is known that inhibition of this enzyme leads to an increase in intracellular calcium due to the increase in sodium calcium exchange, increased entry of calcium via the voltage gated calcium channel and increased release of calcium from intracellular endoplasmic reticulum calcium stores. The increase in intracellular calcium by displacing magnesium from its binding sites leads to a decrease in functional

availability of magnesium. Decrease in magnesium inhibits Na^+-K^+ ATPase further as the ATP magnesium complex is the actual substrate for the reaction. Thus there is progressive inhibition of Na^+-K^+ ATPase.

Nicotine acts on the nicotinic cholinergic receptor which promotes membrane depolarization and increased entry of calcium via the voltage gated calcium channels. Morphine produces hyperpolarisation of the neuronal membrane. This results in Na^+-K^+ ATPase stimulation and reduced opening of the voltage gated calcium channel and decrease in intracellular calcium. Thus increased nicotine can lead on to an intraneuronal calcium overloaded state and functional magnesium deficiency owing to Na^+-K^+ ATPase inhibition.

The changes discussed above are with respect to the RBC membrane. It has been suggested that the changes in the RBC membrane may be reflective of neuronal membrane changes. If similar changes take place in the neuronal membrane also (this can be studied only with isolated neuronal membrane) then the consequence of an inhibition of neuronal membrane Na^+-K^+ ATPase and the resultant increase in the neuronal calcium load and magnesium depletion can be manifold. Na^+-K^+ ATPase inhibition can produce neurotransmitter transport dysfunction, apoptosis and mitochondrial dysfunction, protein processing defects, immune activation and activation of oncogenes as discussed below.

The increased presynaptic neuronal Ca^{++} can produce cyclic AMP dependent phosphorylation of synapsins in the presynaptic neuron resulting in increased neurotransmitter release into the synaptic junction and vesicular recycling. Increased intracellular Ca^{++} in the post synaptic neuron can also activate the G-protein coupled neurotransmitter signal transduction system of monoamine neurotransmitters and also Ca^{++} dependent NMDA signal (glutamate receptor) 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 neurotransmitter (monoamines and glutamate) by presynaptic and glial uptake at the end of synaptic transmission. By these mechanisms, inhibition of Na^{+}-K^{+} ATPase can promote monoaminergic and glutamatergic transmission. Increased glutamatergic transmission resulting in excitotoxicity has been implicated in neuronal degeneration observed in Parkinson's disease, primary generalized epilepsy and schizophrenia. Increased monoaminergic transmission particularly of dopamine in the mesolimbic system has been implicated in schizophrenia. A biphasic response with an increase in monoaminergic transmission in the manic phase and a decrease in the depressive phase has been reported in the MDP. Inhibition of Na^{+}-K^{+} ATPase can also result in defective neuronal membrane repolarisation and a paroxysmal depolarization shift resulting in epileptogenesis.

Increased intracellular Ca^{++} activates the Ca^{++} dependent calcineurin signal transduction pathway which can produce T-cell activation and secretion of interleukin-3,4,5,6 and TNF alpha (Tumour necrosis factor alpha). This can explain the immune activation in MS. TNF alpha binds to its receptor and in turn can activate the caspase cascade, especially the downstream caspase-9 and produce apoptosis. Caspase-9 is an ICE protease which converts the IL-1 beta precursor to IL-1 beta, IL-1 beta produces apoptosis of the neuron in Parkinson's disease and Alzheimer's disease and the oligodendrocyte, the myelin forming cell in MS.

Increased intracellular Ca^{++} can open the mitochondrial PT pore causing a collapse of the H^{+} gradient across the inner membrane and uncoupling of the respiratory chain. This also leads to volume dysregulation and rupture of the Outer membrane of mitochondria resulting in the release of AIF (apoptosis inducing factor) and cyto C (cytochrome C) to the cytoplasm. This results in activation of caspase-9 which produces cell death. Apoptosis has been implicated in neuronal degeneration. Increased neuronal apoptosis can produce

defective synaptogenesis and synaptic connectivity contributing to functional disorders like schizophrenia and epilepsy.

The magnesium deficiency related ATP synthase defect and increased calcium related opening of the mitochondrial PT pore produces a mitochondrial dysfunction. This results in incomplete reduction of O_2 and increased production of the free radical, the superoxide ion. Mitochondrial dysfunction has been implicated in the pathogenesis of neuronal degeneration like the Parkinsons disease. Increased intracellular Ca^{++} can also activate NOS (nitric oxide synthase) causing increased production of NO which combines with the superoxide radical to form peroxynitrite ion promoting lipid peroxidation. Free radical damage has been implicated in oncogenesis and neuronal degeneration.

Intracellular magnesium deficiency also results in defective ubiquitin dependent proteolytic processing of glycoproteins and antigens as it requires magnesium for its function. The protein processing defect can result in defective glycosylation of endogenous myelin glycoprotein antigens with consequent defective formation of the MHC-antigen complex. The MHC linked peptide transporter is a P-glycoprotein which transports the MHC-antigen complex to the antigen presenting cell surface and requires magnesium for its function. Intracellular Mg^{++} deficiency results in dysfunction of MHC linked peptide transport. Defective presentation of endogenous myelin glycoprotein antigen can explain the immune dysregulation in MS. A CD_8 MHC class-1 restricted immune dysregulatory defect has been described in MS. Defective tumour antigen presentation to the NK cell will lead to oncogenesis as cancer cell immunosurveillance becomes dysfunctional. Defectively processed glycoproteins like membrane beta amyloid resist lysosomal digestion and accumulate, producing neuronal degeneration. Ubiquitin dependent proteolytic dysfunction has been reported in neuronal degeneration, especially in Parkinson’s disease. Defective glycoproteins and glycosaminoglycans of the

neuronal membrane can produce defective synaptic connectivity producing functional disorders like epilepsy, MDP and schizophrenia. Defective glycosylation of proteins consequent to Na^{+}-K^{+} ATPase inhibition can result in loss of contact inhibition and oncogenesis.

Increased intra cellular calcium activates phospholipase C beta which results in production of diacyl glycerol (DAG) which activates protein kinase C. The protein kinase C (PKC) activates the MAP kinase cascade resulting in cellular proliferation. The decreased intracellular Mg^{++} can produce dysfunction of GTPase activity of the alpha-subunit of G-protein. This results in ras oncogene activation, as more of the ras is bound to GTP rather than GDP. Phosphorylation mechanism is required for the activation of the tumour suppressor gene P_{53}. The activation of P_{53} is impaired owing to intracellular magnesium deficiency producing a phosphorylation defect.

In syndrome X there is an increase in depolarising nicotinergic transmission. This can lead to Na^{+}-K^{+} ATPase inhibition. The consequent increase in calcium within the cell especially the beta cell can displace magnesium from the binding site. Magnesium depletion within the beta cell can lead to increased release of insulin from the beta cell. A cellular magnesium deficiency and increase in a calcium overloaded state can have the following consequences. Increase in intracellular calcium can lead to immune activation and increased production of TNF alpha leading to insulin resistance. Intracellular cellular magnesium deficiency can lead to protein tyrosine kinase dysfunction, an insulin receptor defect. Increased intra cellular calcium can lead to increase G-protein coupled signal transduction of the contrainsulin hormones-glucagon, growth hormone and adrenaline. This leads to hyperglycemia. Increased intra cellular calcium can open up the mitochondrial PT pore producing a mitochondrial dysfunction and uncoupling oxidative phosphorylation. Decreased intra cellular magnesium can inhibit ATP synthase producing a decrease in synthesis of ATP and a

mitochondrial dysfunction. Decreased intracellular magnesium can lead to inhibition of glycolysis and citric acid cycle. Thus glucose utilization as a whole is decreased. Intra cellular magnesium deficiency can produce decreased dolichol phosphate synthesis and N-linked glycosylation. Generation of ATP for synthesis of nucleoside diphosphate sugars for O-linked glycosylation is also defective leading to altered glycoproteins. Intracellular magnesium deficiency can also upregulate GAG synthesis. Both these contribute to the microangiopathy and macroangiopathy of syndrome X. Increased intracellular calcium can increase the signal transduction of the G-protein coupled platelet activating factor receptor and thrombin receptor producing thrombosis. Intracellular magnesium deficiency can also produce vasospasm described in syndrome X.

Nicotine by its CNS stimulant action has been reported to promote epileptogenesis. The increased depolarising nicotinergic transmission producing net Na^+-K^+ ATPase inhibition can contribute to epileptogenesis. Inhibition of Na^+-K^+ ATPase can lead to a paroxysmal depolarisation shift and epileptogenesis. Nicotine, by interacting with nicotinic receptors, can facilitate the release of dopamine, promoting the dopaminergic transmission in the brain. The dopaminergic hyperactivity in schizophrenia could be due to increased nicotine synthesis. Increased levels of nicotine have been detected in the serum of manic depressive psychosis patients. Nicotine has a biphasic effect on limbic dopaminergic and serotoninergic transmission with initial activation followed by significant inhibition later. This could contribute to the excessive monoaminergic transmission during the manic phase and reduced monoaminergic transmission during the depressive phase of bipolar mood disorder. Increased nicotinic cholinergic transmission can contribute to the tremor of Parkinson's disease. Nicotine may contribute to hypertension and hypertriglyceridemia observed in syndrome X by the vasospasm it produces and its reported effect on lipid metabolism respectively. No nicotine could be detected in MS.

In this context it is pertinent to note the interrelationship between these diseases as documented in literature. Autoantibodies have been demonstrated in MS, SLE, motor neuron disease (MND), Alzheimer's disease, Down's syndrome, paraneoplastic disease and AIDS dementia. Psychosis has been described in neurolupus, MS, Alzheimer's disease, Parkinson's disease, cancer related psychosis and AIDS dementia. The relationship between Hodgkin's lymphoma and MS, lymphoma and MND, CNS lymphoma and HIV infection and lymphomatous transformation in SLE and rheumatoid arthritis have been documented. Viral persistence as an etiological factor has been documented in MS, Parkinson's disease, non-Hodgkin's lymphoma and schizophrenia. Hyperinsulinemia has been documented in Alzheimer's disease and immune mediated neuropathies described in syndrome X. This interrelationship is possibly dependent on increased nicotine synthesis contributing to Na^+-K^+ ATPase inhibition.

References

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