Chapter 7

Archaeal Morphine - Description of Hypo - and Hyper - Morphinergic State in Relation to Neuropsychiatric Diseases

Introduction

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 higher affinity morphine receptor type is mu1 and the lower affinity morphine-selective type is mu_2. Recently Stefano has proposed the presence of a third mu_3 receptor to which morphine binds exclusively.

It was suggested that as a class, the catecholaminergic neuron may give rise to dopamine, norepinephrine, epinephrine and morphine from tyrosine. Morphine immunoreactivity has been found in the hippocampus as well as in the mesocorticolimbic and mesostraital regions and morphine produces reinforcement associated with increased ventral tegmental area dopaminergic (VTA DA) neuron firing activation of the mesolimbic pathway and an increase in nucleus accumbers (NAS) extracellular dopamine (DA) concentration.

Morphine plays a role in immunoregulation. Injection of vertebrate animals with morphine resulted in deficient macrophage function and alteration of T-cell activity. Morphine tended to inhibit or reduce immunocyte activity, i.e. chemotaxis, cellular velocity, phagocytosis and cellular responsiveness to peptidergic signals. Opioid peptides are involved in regulation of the stress response and insulin induced hypoglycemia is associated with a 20% rise in CSF beta endorphin concentration'. It has also been noticed that rat C-6 glioma cells contain opiate alkaloid binding receptor sites and it has been proposed to mediate an inhibitory effect of morphine of cell proliferation and metastasis.

In this context it was considered pertinent to look for endogenous morphine 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 as morphine is synthesized from the former.

Results

No morphine could be estimated in the serum of control subjects and the serum of patients with epilepsy, Parkinson's disease, schizophrenia, CNS glioma and syndrome X also showed no peak corresponding to morphine. Serum of patients with MDP contained 9.56 μg/dl while that of multiple sclerosis had 9.92 μg/dL.

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 sodium potassium 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. The absence of morphine in most disorders studied is a reflection of low tyrosine and dopamine levels, which are the

precursors of morphine. However, the presence of morphine in MDP and MS inspite of decreased tyrosine levels requires further study.

The inhibition of membrane Na^+-K^+ ATPase activity in most of the disorders studied is another significant observation. This inhibition can result from decreased hyperpolarising morphinergic transmission. It is known that inhibition of this enzyme leads to increase in intracellular calcium due to increase in sodium calcium exchange, increased entry of calcium via 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.

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 reduced morphine 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 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 monoamlnerglc transmission particularly of dopamine in the mesolimbic system has been implicated in schizophrenia. A biphasic response with increase in monoaminergic transmission in the manic phase and 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. 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 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 free radical, the superoxide ion. Mitochondrial dysfunction has been implicated in the pathogenesis of neuronal degeneration like in Parkinson's disease. Increased intracellular Ca^{++} can also activate NOS (nitric oxide synthase) causing increased production of NO which combines with 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 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. The results in ras oncogene activation, as more of the ras are 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 a reduction in hyperpolarising morphinergic 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 on 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 the citric acid cycle. Thus glucose utilisation 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 on to altered glycoproteins. Intra cellular 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.

The decreased hyperpolarising, morphinergic 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. No morphine was detected in epilepsy. No morphine was detected in schizophrenia possibly due to low tyrosine levels noted in the serum of these patients. Increased level of morphine has been detected in the serum of manic depressive psychosis patients. Morphine 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. Morphine suppresses tumour growth and metastases while nicotinic cholinergic transmission promotes cellular proliferation. Morphine deficiency and nicotinic excess could thus contribute to genesis of gliomas. No morphine could be detected in PD and the protective of effect of morphine on intraneuronal calcium load is lost. Morphine deficiency was noticed in syndrome X. Intrathecal morphine administration produces hypoglycemia via spinal opiate and central alpha-adrenergic receptors. Morphine also stimulates insulin release from the beta cells. Thus morphine deficiency can contribute to the hyperglycemia of syndrome X.

The detection of increased levels of morphine in multiple sclerosis is significant. Morphine has an immunoregulatory function in the brain and has been found to inhibit the expression of antigenie markers in T-helper and T-suppressor cells. Morphine may contribute to this CD_8 MHC class-1 restricted T-cell defect described in multiple sclerosis. Serum of patients with MS showed strychnine which can produce an increase in the intraneuronal calcium load producing oligodendrocyte apoptosis and immune activation.

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 has 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 the immune mediated neuropathies described in syndrome X. This interrelationship is possibly dependent on reduced morphine contributing to Na^+-K^+ ATPase inhibition.

References

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