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A REVIEW ON THE MPTP NEUROTOXIN INDUCED PARKINSON'S DISEASE

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INTRODUCTION

In 1976, MPTP was incidentally discovered by a chemistry student, who was trying to synthesize a synthetic heroin.[1] Others, addicted to heroin, replicated this mistake in the early 1980s and developed severe PD-like symptoms. Dr. Langston recognized the potential of this toxin for creating a valid disease model andsoon identified the effects of MPTP administration in non-human primates and described the impairments that resembled the motor disabilities of idiopathic PD.[2] In 1986, Sonsalla and Heikkila[3] showed that MPTP could have many of the same effects in mice. MPTP is highly lipophilic in nature thus it can easily cross the blood brain barrier, where it binds mainly in astrocyte lysosomes, and there is general agreement that astrocytes convert MPTP to its toxic metabolite, the 1-methyl-4-phenylpyridinium (MPP^+) ion.[4,5] Evidence indicates that MPTP enters the glial cells in the striatum or the substantia nigra, where it is cleaved by the monoamine oxidase-B isozyme to form MPP^+ (l-methyl-4- phenylpyridinium), the neurotoxic metabolite. MPP^+ is known to be anexceptional substrate for the dopamine transporter (DAT), which explains its selectivity for dopaminergic neurons.[6, 7]

The MPTP model has been one of the most accurate models of human idiopathic PD and has contributed to the understanding of the course and cause of PD. MPTP is a neurotoxin accidentally discovered in laboratory that targets the dopaminergic neurons within the nigrostriatal pathway and produces an array of clinical and pathological features that nearly simulate idiopathic Parkinsonism symptoms.

Future scope of the study involves improvement in the screening and the evaluation of Anti-Parkinsonian drugs and developmental processes. MPTP model can prove to be helpful in

understanding mechanisms for the death of dopamenergic neurons. Therefore it is essential to investigate in MPTP animal model to understand the involvement of mitochondrial dysfunction, energy (ATP) depletion, free-radicals production, apoptosis, and glutamate excitotoxicity in pathogenesis of PD.

Fate of striatal MPP^+

Striatal MPP^+ is taken up through the dopamine transporter of dopaminergic neurons and routed in a worsening fashion to the cell bodies. It is reported that MPP^+ is an effective inhibitor of complex I respiration in isolated mitochondria.[8] MPP^+ is imported into mitochondria where it binds to NADH dehydrogenase in complex I of the oxidative electron transport chain inhibiting mitochondrial respiration.[9,10]

MPP^+ promotes oxidative stress

Inhibition of mitochondrial respiration results into increased oxidative stress through the production of toxic free radicals.[11] As a result, adenosine triphosphate (ATP) decreases rapidly in the striatum and substantianigra pars compacta (SNpc) regions of the brain, which are more susceptible to MPTP-induced neurotoxicity.[12] Remarkably, a significant ATP depletion can result from as little as 25% inhibition of complex I.[13] Following exposure to MPTP or MPP^+, the hydropyridine or its metabolite is cleared from the brain within 12 hours, and the depletion of ATP is no longer evident 24 hours after administration.[14] However, the actual neuronal deterioration seems to take a longer period of time.[15] In Parkinson's disease, it is accepted that oxidative stress is critically involved in the dopaminergic neuron death since the SN of PD patients exhibits increased levels of oxidized lipids, proteins and DNA and a decrease in the levels of glutathione (GSH).[16] There is evidence of oxidative stress in the brains of PD patients. Oxidative stress has received the most attention in PD because of the potential of the oxidative metabolism of dopamine to yield hydrogen peroxide (H_2O_2) and other reactive oxygen species (ROS). Sufficient data is available which indicates the presence of increased levels of malondialdehyde (MDA) and lipid hydroperoxide, products of lipidperoxidation in the substantianiagra pars compacta (SNc) region in the brain of PD patient.[17]

MPTP induced neuronal injury and ATP depletion

Following MPTP treatment axonal degeneration was evident at all stages of the time course in the form of myelin separation, demyelination, localized cytoplasmic shrinkage, mitochondrial disruption, or microtubule and neurofilament disturbance. MPTP has been

shown to accumulate within the mitochondria as MPP^+, which, through its interaction with complex I, causes a reduction in mouse striatal and midbrain ATP levels.[18] This reduction in conjunction with the increased generation of reactive oxygen species most likely results in the ultrastructural abnormalities that befall mitochondria and the rest of thecell.Impaired mitochondrial function leads to oxidative stress, deficits in ATP synthesis, and α-synuclein aggregation, which may contribute to Parkinson's disease.[19]

MPTP induced mitochondrial dysfunctioning

MPP^+ is subsequently taken up selectively by dopaminergic terminals and concentrated in neuronal mitochondria in the SNpc. The mitochondrion is the primary site for the generation of cellular energy, regulated by five respiratory chain complexes. Complex I control the transfer of one electron from NADH to co-enzyme Q and the transfer of two protons to the mitochondrial inter-membrane space, which are then used by complex V to synthesize ATP from ADP, the main energy supply of the cell. MPP^+ binds to NADH dehydrogenase and inhibits complex I of the electron transport chain. MPP^+ can increase leakage of electrons at complex I, thereby increasing mitochondrial generation of superoxide. Complex I inhibition results in incomplete oxygen reduction and in generation of potentially harmful ROS, including superoxide, hydrogenperoxide (H_2O_2) by action of superoxide dismutases and hydroxyl radicals generated by iron-mediated Fenton reaction. MPTP causes irreversible inactivation of complex I by generating free radicals.[20,21,22,23,24] The toxicity of MPP^+ seems to result from its inhibition of mitochondrial respiration at the level of complex I, resulting in a rapid fall in ATP levels and eventual cell death due to energy failure.[25] In PD, mitochondrial Complex I activity decreases in the substantia nigra, an effect which is specific to PD. Therefore a mitochondrial complex I defect may cellular degeneration in PD through decreased ATP synthesis.[26]

MPTP treatment up regulate components of the mitochondrial apoptotic cascade

A complex I defect may aggravate the occurrence of apoptosis. As complex I is a main site of proton pumping, a complex I defect in PD may contribute to neuronal susceptibility and may lead to apoptosis. It is well proven that a reduction in the mitochondrial membrane potential may result in impaired proton pumping, which may lead to the opening of mitochondrial permeability transition pores and the release of small mitochondrial proteins that signal for the onset of apoptosis. The complex I activity of the mitochondrial respiratory chain decreases by 30–40% in the SNc region of the PD patients. The mitochondrial apoptotic

cascade has been suggested to play an important role in MPTP induced DAergic neurotoxicity.[27] MPTP treatment up regulate components of the mitochondrial apoptotic cascade, including cytochrome c and caspase-9 in the substantia nigra (SN). The neuronal expression of p35, a potent and irreversible caspase inhibitor, and overexpression of the anti-apoptotic protein, Bcl-2, conferred a resistance to MPTP-induced neurotoxicity.[28] Mitochondrial apoptotic pathway requires the release of cytochrome c from mitochondria in connection with opening of the mitochondrial transition pore. Importantly, MPP^+ induces the opening of the mitochondrial transition pore through the inhibition of complex I and the production of ROS.[29] After cytochrome c is released, it then forms a complex with apoptosis protease activating factor 1 and pro- caspase-9, which results in caspase-9 activation followed by activation of downstream caspases.[30]

Effects of MPTP on dopamine, a major neurotransmitter of extrapyramidal system

MPP^+ stimulates the release of DA.[31] Excessive auto-oxidation of both intracellular and extracellular DA results in the formation of cytotoxic quinones and highly reactive •OH. Excessive formation of •OH, which has a very short half-life and interacts close to their site of generation in vivo can cause cell damage through chain reactions leading to membrane lipid peroxidation, alterations in membrane fluidity[32,33] protein cross-linking, and DNA damage, which is mediated by base pair mutations[34] Overproduction of •OH, may devastate cellular antioxidant defense mechanisms andmay contribute to the death of DAergic neurons.[35]

Effect of MPTP on neurotransmitter level of Glutamate

There is proof that supports the idea of excitotoxicity contributing to MPTP-induced DAergic neuron death. The depletion of cellular ATP caused by inhibition of complex I of the electron transport chain in mitochondria results in depolarization of the membrane potential of SNpc neurons and an increase in extracellular glutamate levels which, in turn, stimulates N-methyl-D-aspartate (NMDA) receptors on the DAergic neurons. MPTP treatment leads to an increase in the affinity for glutamate by glutamate transporters in the SNpc. The glutaminergic sources contributing to these enhanced levels are not known, but could include glia in the surrounding areas, enhanced cortical or subthalamic release from axon terminals on DAergic neurons and/or arise from an exchange with the glutamate/cystineantiporter, which exchanges glutamate from the cytoplasm of the nerve terminal, although the latter remains controversial.[36, 37] In particular, the substantianigra receives rich glutamatergic inputs from

both the neocortex and subthalamic nucleus. Activation of NMDA receptors allows an influx of calcium followed by activation of nitric oxide synthase (NOS), increasing the generation of toxic free radicals through the peroxynitrite reaction and thus may contribute to Parkinson's disease.

Role of NO^- in MPTP-inducedneurotoxicity

The stimulation of NMDA receptors by extracellular glutamate results in an elevation of intracellular Ca^{2+} via the opening of Ca^{2+} channels due to an inability of the cell to sequester and pump out Ca^{2+}[38] Elevation of intracellular Ca^{2+} in SNpc neurons activates neuronal nitric oxide synthase (nNOS) and NO is synthesized. NO plays a key role in MPTP-induced neurotoxicity. NO reacts with O^{2-} to form peroxynitrite ($ONOO^-$).Once formed, $ONOO^-$ can diffuse over several cell diameters where it can oxidize lipids, proteins, and damage DNA.[39] DNA damage, in turn, activates the DNA damage sensing enzyme poly (ADP-ribose) polymerase (PARP).[40] PARP activation induces PAR polymers and depletes nicotinamide adenine dinucleotide(NAD^+) and ATP.[41] ThegenerationofPARpolymers, theribosylation of proteins, and the loss of NAD^+ and ATP signal to the mitochondria induce apoptosis inducing factor (AIF) release and translocation.[42] AIF, a mitochondrial flavoprotein that mediates caspase-independent cell death translocates from the mitochondria to the nucleus to induce DNA fragmentation and nuclear condensation.[43,44] The disassembling of the nuclear structure ultimately leads to celldeath.7-Nitroindazole (7-NI), which is a selective inhibitor of the neuronal isoform of nitric oxide synthase (NOS) is reported to block MPTP neurotoxicity in mice, thus implicating that inhibitors of neuronal NOS might be useful in the treatment of Parkinson's disease.[45]

Precipitation of Inflammation in MPTP-inducedneurotoxicity

MPTP administration may provoke an inflammatory reaction by initiating permeation of T cells into the SN and striatum, activation of the resident brain macrophages, microglia, and increased gene expression of the pro-inflammatory cytokines interleukin-1 β (IL-1β), tumor necrosis factor α (TNFα), and interferon γ (INFγ).[46] Furthermore, activated microglia can be phagocytic and release pro-inflammatory factors such as TNFα, prostaglandin E2 (PGE2), INFγ, and ROS such as NO^-, H_2O_2, and O^{2-}, which are all toxic to neurons.[47] Importantly, following MPTP treatment, microglial cell activation occurred prior to DAergic neuron death in the SNpc. Furuya and colleagues reported that caspase-11, which is predominantly expressed in microglia in the SN, can produce cell death by regulating the expression of

cytotoxic cytokines. Caspase-11 null mice were resistant to the neurotoxic effects of an acute MPTP treatment.[48] Interestingly, inhibition of microglia activation relieved the degeneration of DAergic neurons.[49] Furthermore, NO, a lipophilic radical that is toxic to neurons, is one of the pro-inflammatory factors released by microglia. Inducible nitric oxide synthase (iNOS) is upregulated in MPTP-treated mice resulting in elevated NO production. The expression of iNOS in activated microglia contributes to the death of DAergic neurons in MPTP toxicity[40, 50] Abnormal protein interactions in the ubiquitin- proteasome system (UPS), which degrades short-lived, damaged, and misfolded proteins in an ATP-dependent manner has been proposed as a mechanism of DAergic neuron death in the SNpc. In support of this hypothesis, systemic administration of a proteasome inhibitor led to degeneration of the nigrostriatal pathway.[51, 52] In addition, chronic treatment of MPTP in mice is known to cause a continuing inhibition of the UPS and cause degeneration of DAergic neurons in the SN.[53]

It has been proposed that Lewy bodies develop gradually, appearing first as insoluble proteinaceous granules intermingled with filaments that are both ubiquitin and α-synuclein positive. Neither Lewy bodies nor inclusions that resemble these bodies were observed when mice were acutely or subchronically (subacutely) treated with MPTP.[54] However, chronic MPTP administration results in the formation of α-synuclein positive granular aggregates.[55] Chronic and continuous MPTP administration in mice produced inclusion bodies in remaining neurons in the SN.[56] Furthermore, chronic treatment of MPTP and probenecid (MPTP/P) to mice, showed the accumulations of α-synuclein and ubiquitin in the surviving DA neurons.[57] Inflammation has also been proposed as a possible mechanism in the pathogenesis of PD. Activated microglia have been observed in the substantianigra, putamen, where DA loss is prominent, and also in the hippocampus of patients with PD.[58] which has been suggested to be responsible for neuronal dysfunction and cognitive decline in PD. Activated microglia produces a variety of inflammatory cytokines, including interleukin (IL)-2.[59] Increased levels of inflammatory cytokines have also been found in the nigrostriatal regions and in cerebrospinal fluid (CSF) of patients with PD.[60]

Advantages of MPTP model over other neurotoxin models of PD

Despite numerous efforts to develop progressive toxic protocols in mice, few fully reflect the hallmarks of the disease. Mouse models using 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) are among the most widely used. MPTP mouse models have shed light on the pathophysiology as well as some of the causes of the disease.MPTP model has provided

investigators with a relieable and valid model for studying symptomatic relief and neuroprotective effect of drugs. MPTP, resembles a number of known environmental compounds, including herbicides such as paraquat and the garden insecticide/fish toxin, rotenone; both have been shown to induce dopamine (DA) neuron degeneration.[61, 62, 63, 64] As compared to other neurotoxins MPTP is highly lipophilic and easily crosses the blood brain barrier more readily, where it binds mainly in astrocyte lysosomes, where astrocytes convert MPTP to its toxic metabolite, the 1-methyl-4-phenylpyridinium (MPP^+) ion.[65]

Rationale for developing MPTP model of PD

Animal model systems are the closest to humans that we are able to study. In orderto understand the pathogenesis of this disease, a number of animal models are developed. With using model of toxins, it is possible to develop a progressive model by tempering the toxic doses. The principal advantage of MPTP model is that the behavioral syndrome closely resembles the clinical features of idiopathic PD. The systemic model has partial dopaminergic denervation bilaterally and probably best represents the degree of loss seen in all stages of PD, including end-stage disease where some dopaminergic neurons are still present. The administration of MPTP to mice results in behavioral alterations that may resemble human parkinsonism. For example hypokinesia, bradykinesia, and akinesia can be observed through various behavioral analyses including open field activity monitoring, swim test, pole test, grip coordination, and rotorod. The MPTP-lesioned mouse model has proven valuable to investigate potential mechanisms of neurotoxic induced dopaminergic cell death. For example, mechanisms under investigation have included mitochondrial dysfunction, energy (ATP) depletion, free-radical production, apoptosis, and glutamate excitotoxicity. In addition to its utility in studying acute cell death, the MPTP-lesioned model also provides an opportunity to study injury-induced neuroplasticity. The MPTP-lesioned mouse displays the return of striatal dopamine several weeks to months after lesioning. MPTP model is well suited for therapeutics that interact with remaining dopaminergic neurons, including growth factors, neuroprotective agents, and dopamine modulation. The easily reproducible dyskinesia in this model allows for extensive investigation of its underlying mechanism and treatment.

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