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Review

Methamphetamine-induced neurotoxicity: the road to Parkinson's disease

Bessy Thrash, Kariharan Thiruchelvan, Manuj Ahuja, Vishnu Suppiramaniam, Muralikrishnan Dhanasekaran

Department of Pharmacal Sciences, Harrison School of Pharmacy, Auburn University, 4306 Walker building, AL 36849 Auburn, USA

Correspondence: Muralikrishnan Dhanasekaran, e-mail: dhanamu@auburn.edu

Abstract:
Studies have implicated methamphetamine exposure as a contributor to the development of Parkinson's disease. There is a significant degree of striatal dopamine depletion produced by methamphetamine, which makes the toxin useful in the creation of an animal model of Parkinson's disease. Parkinson's disease is a progressive neurodegenerative disorder associated with selective degeneration of nigrostriatal dopaminergic neurons. The immediate need is to understand the substances that increase the risk for this debilitating disorder as well as these substances' neurodegenerative mechanisms. Currently, various approaches are being taken to develop a novel and cost-effective anti-Parkinson's drug with minimal adverse effects and the added benefit of a neuroprotective effect to facilitate and improve the care of patients with Parkinson's disease. A methamphetamine-treated animal model for Parkinson's disease can help to further the understanding of the neurodegenerative processes that target the nigrostriatal system. Studies on widely used drugs of abuse, which are also dopaminergic toxicants, may aid in understanding the etiology, pathophysiology and progression of the disease process and increase awareness of the risks involved in such drug abuse. In addition, this review evaluates the possible neuroprotective mechanisms of certain drugs against methamphetamine-induced toxicity.

Key words:
drug abuse, methamphetamine, neurotoxin, Parkinson disease, neuroprotection

Introduction

Methamphetamine is a psychostimulant and a common drug of abuse. Recently, increased methamphetamine use, which leads to dependence or addiction, has become a major health concern worldwide. However, methamphetamine has been used in clinical settings as a treatment for narcolepsy and attention deficit hyperactivity disorder (ADHD) in children, [85]. For these pathological conditions, it is considered a second line of treatment that is used when amphetamine and methylphenidate cause severe and numerous adverse effects. It is also used for weight loss and to maintain alertness, focus, motivation, and mental clarity for extended periods of time, as well as for recreational purposes. Methamphetamine easily crosses the blood-brain barrier, enters the brain and triggers an immediate signaling cascade, which releases monoamines (dopamine, norepinephrine and serotonin). It can also act as a dopaminergic and adrenergic reuptake inhibitor and, at high concentrations, as a monoamine oxidase inhibitor. The major dopaminergic pathways in the brain are the nigrostriatal, mesolimbic, meso-

cortical and tuberoinfundibular pathways. Methamphetamine significantly stimulates the mesolimbic reward and nigrostriatal pathways. Stimulation of the mesolimbic reward pathway by methamphetamine causes euphoria and excitement; thus, people are prone to abuse the drug and become addicted to it. [27].

Methamphetamine affects the biochemical mechanisms responsible for regulating heart rate, body temperature, blood pressure, appetite, attention, mood and responses associated with alertness and alarm conditions. The acute physical effects of the drug closely resemble the physiological and psychological effects of an epinephrine-provoked fight-or-flight response, including increased heart rate and blood pressure, vasoconstriction, bronchodilation, and hyperglycemia.

Methamphetamine is a neurotoxin, as evidenced by the dopaminergic neurodegeneration it causes in rodents and primates [19, 47]. It has been proposed that dopamine plays a crucial role in methamphetamine-induced neurotoxicity because experiments that reduce dopamine production or block its release demonstrate a decrease in the toxic effects of methamphetamine. High doses as well as chronic administration (low dose) of methamphetamine produce losses in several markers of central monoaminergic neurons, specifically the dopaminergic and serotoninergic neurons. Dopamine and serotonin concentrations, their uptake sites and their precursor enzyme activities (tyrosine and tryptophan hydroxylase) are reduced by methamphetamine. Dopamine metabolism generates reactive oxygen species such as hydrogen peroxide, hydroxyl radicals, semiquinones and superoxide anions. Hence, there is a strong possibility that oxidative stress, which occurs immediately after methamphetamine administration, mediates neurotoxicity [114]. The long-lasting damage to nigral neurons mimics the neurodegenerative process of Parkinson's disease. Therefore, methamphetamine is an ideal toxic candidate to produce an animal model of Parkinson's disease. Gaining a better understanding of the neurodegeneration in the nigrostriatal system associated with Parkinson's disease may be useful in investigating pharmacological agents for neuroprotective or neurorestorative effects. This may lead to the development of much needed novel therapeutic agents and even to a proactive treatment strategy for Parkinson's disease. Hence, a methamphetamine-treated animal model may be used to study the mechanisms of dopaminergic neurodegeneration and aid in the development of therapeutic interventions for Parkinson's disease [34, 57, 62, 63, 86, 105].

Methamphetamine

Methamphetamine is a central nervous system (CNS) stimulant that can be synthetically prepared by catalytic hydrogenation of ephedrine or pseudoephedrine. Methamphetamine is similar in structure to other CNS stimulants such as amphetamine and methcathinone, which are also produced from ephedrine and pseudoephedrine by chemical reduction. Thus, methamphetamine is a synthetic stimulant, as opposed to drugs obtained from natural resources, such as cannabinoids (derived from *Cannabis sativa*) and cocaine (derived from *Erythroxylon coca*).

The methyl group present in methamphetamine makes the molecule more lipophilic and thus facilitates transport across the blood-brain barrier. It also increases the resistance against enzymatic degradation by monoamine oxidase. Methamphetamine causes the dopamine, norepinephrine and serotonin (5-HT) transporters to reverse their direction of flow. This inversion leads to a release of these transmitters from the vesicles to the cytoplasm and from the cytoplasm to the synapse, causing increased stimulation of post-synaptic receptors. Methamphetamine also indirectly prevents the monoamine reuptake of these neurotransmitters, causing them to remain in the synaptic cleft for a prolonged period [84, 87]. Methamphetamine effects on the body include acute central nervous system stimulation and cardiotoxicity, including induction of tachycardia, arrhythmias, hypertension and cardiovascular collapse (Fig. 1). The drug has a high risk of dependency and abuse, and its widespread abuse has been a growing problem in recent years. It is a highly addictive stimulant with acute and chronic neurotoxic properties. The effects of abuse of this drug include memory loss, aggression, psychotic symptoms and behavioral abnormalities, and potential heart and brain damage [76]. Effects on the CNS include tremors, restlessness, agitation, insomnia, increased motor activity, headache, convulsions, and coma. Psychiatric side effects include agitation, confusion, mood elevation, delusions, paranoia, increased wakefulness, talkativeness, irritability and panic attacks.

A withdrawal syndrome occurs after abrupt cessation following chronic use [9]. Moreover, withdrawal from methamphetamine dependence is distinguished by protracted anhedonia, dysphoria and severe cravings, and is also characterized by excessive sleeping,

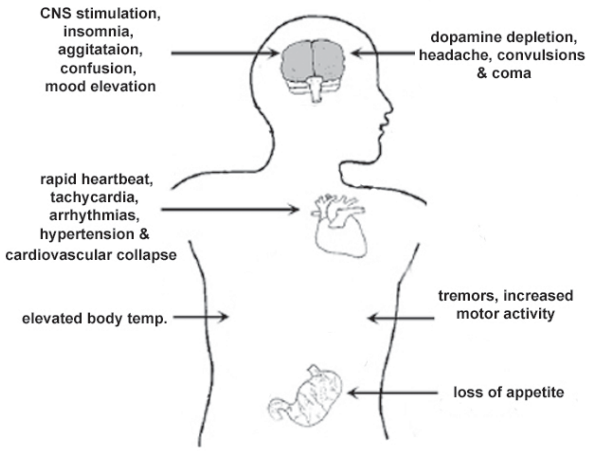

Fig. 1. Methamphetamine-induced toxicity in the body

eating, and depression-like symptoms, often accompanied by anxiety [71]. Withdrawal symptoms of methamphetamine can be reduced by pharmacological or non-pharmacological approaches. Psychosocial behavioral therapy and contingency reward therapy have been successfully used in patients addicted to methamphetamine. Similarly, opioid receptor antagonists and antidepressants have been used to reduce the severe withdrawal symptoms related to methamphetamine.

Mechanisms of methamphetamine toxicity

Methamphetamine increases the auto-oxidation of dopamine, leading to increased signaling of oxidative stress [99, 118]. As methamphetamine is a cationic lipophilic molecule, it can diffuse into the mitochondria and be retained in the mitochondrial cytoplasm for an extended period of time. As such, it enters into the brain rapidly and displaces dopamine in the vesicles, releasing it into the synaptic cleft *via* dopamine transporter (DAT)-mediated outward transport. Because methamphetamine displaces the dopamine in the vesicles, large amounts of dopamine are released into the synaptic cleft and cytosol, where it then undergoes auto-oxidation. During the auto-oxidation, synthesis and metabolism of dopamine, hydrogen peroxide is produced as a by-product by tyrosine hydroxylase and monoamine oxidase. The hydrogen peroxide, which can react nonenzymatically to form highly reactive hydroxyl radicals, then takes part in a positive feedback loop, causing further progression of oxidative damage [48]. In addition, dopamine can be rapidly oxidized into quinones and semiquinones, which are then converted into toxic radicals such as superoxide and nitrogen radicals through redox cycling. These radicals create further oxidative stress [37, 99, 118]. Once formed, free radicals interact with sugars, proteins and lipids, creating a number of modifications. Mitochondrial DNA is sensitive to reactive oxygen species because mitochondria have only a limited arsenal of DNA repair processes. Therefore, mitochondrial DNA mutations can cause defects in the respiratory chain function, leading to severe cellular damage. Several studies on methamphetamine have shown the generation of reactive radicals that are capable of causing mitochondrial dysfunction, reduced energy metabolism, apoptosis and eventual cell death [32, 45, 82, 86].

Further studies have demonstrated a link between oxidative damage and protein aggregates, which are characteristic features of Parkinson's disease [49]. Evidence shows that oxidative damage impairs ubiquitination and degradation of proteins by proteasomes. This may aid in the aggregation of α-synuclein, which is the main protein that forms eosinophilic inclusions known as Lewy bodies, a pathological hallmark of Parkinson's disease. The formation of these Lewy bodies is a key determinant that differentiates this disorder from other neurodegenerative diseases [66]. Upregulation and increased aggregation of α-synuclein was also seen after the administration of neurotoxins [11].

Methamphetamine is thought to cause mitochondrial dysfunction by disrupting the electron transfer chain. Mitochondrial dysfunction has long been thought to play a significant role in the depletion of nigral neurons, leading to dopaminergic depletion. Oxidative stress can cause an inhibition of mitochondrial ATP production, a major determinant of lethal cell injury. Various studies have shown that cells can be protected from injury as long as ATP levels are maintained at a steady state. This hypothesis has been supported by a study that used fructose to maintain ATP and, thus, increased cell survival [46]. The study, therefore, indicates that the loss of ATP is a central mechanism of cell death. Due to its physical property, methamphetamine diffuses into the mitochondria, and the buildup of positively charged particles in the mito-

chondria interferes with the chemical gradient needed by the electron transport chain. Displacement of Ca^{2+} ions stored in the endoplasmic reticulum causes an influx into the mitochondria. The release of these ions results in the activation of pro-apoptotic factors such as caspase-3 and cytochrome-c and disrupts cellular metabolism [12, 19]. This interferes with both the mitochondrial membrane and ATP synthetase, which then causes the initiation of the apoptotic process [16, 19]. This apoptotic process is particularly harmful because the central dopaminergic system, which plays an important role in motor activity, is comprised of a surprisingly small number of neurons. Thus, it is especially vulnerable and even minor insults may lead to irreparable functional deficits [31].

Excitotoxicity is strongly suggested to be involved in the pathogenesis of Parkinson's disease and in methamphetamine-induced neurotoxicity [65]. High levels of oxidative stress set off a chain of events that lead to deficits in mitochondrial function, disruption of the electron transport chain and initiation of excitotoxicity [25]. Excitotoxicity is a process whereby the prolonged or excessive activation of excitatory amino acid receptors leads to an irreversible process of cell death. It is caused when excessive glutamate is released to activate receptors of the N-methyl-D-aspartic acid (NMDA) subtype. Dopaminergic neurons in the substantia nigra are rich in glutamate receptors and are thus highly susceptible to excitotoxicity. Normal stimulation of these receptors enhances dopamine release and synthesis within the striatum, which is important for striatal function. However, if released in excess, glutamate becomes cytotoxic. Methamphetamine causes a release of excess glutamate into the striatum *via* a direct pathway. Mitochondrial dysfunction, as seen in both Parkinson's disease and methamphetamine toxicity, can lead to excitotoxicity as a reduction in ATP results in a loss of the ATP-dependent Mg-blockade of NMDA receptors, causing physiological concentrations of glutamate to mediate a calcium influx into the cell [5, 90]. The resulting rise in calcium increases nitric oxide synthase. This increases the production of nitric oxide (NO), which reacts with the superoxide radical to form peroxynitrite and the hydroxyl radical, both powerful oxidizing agents [22]. This increase in free radical formation has been seen in other toxins used to create animal models for Parkinson's disease. For example, it has been shown that excessive MPP^+ concentrations promote excitotoxicity by enhancing glutamate release [14]. As mentioned previously, dopaminergic neurons in the substantia nigra are rich in glutamate receptors and thus are highly susceptible to excitotoxicity. This emphasizes the importance of a greater understanding of the role of excitotoxicity in Parkinson's disease and methamphetamine toxicity. It also supports the idea of NMDA receptors as possible targets for therapeutic intervention.

Neuroinflammation is another mechanism thought to be involved in neurodegeneration. Neuroinflammation involves the activation of the brain immune cells microglia. Activation of these cells can be beneficial in the protection of the cells, but it can also release neurotoxic cytokines, which could have a deleterious effect and produce neurodegeneration [64]. The neurodegeneration seen with acute administration of methamphetamine has been suggested to be associated with the induction of cyclooxygenase (COX), which causes a neuroinflammatory process that result in deleterious events in the cell [117]. Similarly, there is increasing evidence that one contributor to the later stages of Parkinson's disease is the inflammation of neuronal tissue caused by exposure to microorganisms, toxicants, or environmental factors in early life. Researchers have examined neuroinflammation as a risk factor for Parkinson's disease for quite some time [59]. The substantia nigra has the highest density of microglia in the brain, and studies have shown that Parkinson's disease patients have an even higher number of reactive glial cells than do patients without the disease [70]. The involvement of inflammation in neurodegeneration is supported by several studies. Rotenone, a dopaminergic neurotoxin, increases neurodegeneration in the presence of glia, and non-steroidal anti-inflammatory drugs have been shown to provide neuroprotection against this neurotoxin [104].

Apoptosis, or programmed cell death, is a gradual, progressive cell death. It is characterized by marked cell shrinkage, fragmentation of nuclear DNA and phagocytosis [63]. Because of its central position in the metabolism of the cell, the mitochondrion plays a central role in apoptosis. Mitochondria affect apoptosis through their roles in regulating ATP levels, maintaining the mitochondrial membrane potential, and the release of proapoptotic factors. Mitochondrial dysfunction leads to the cessation of electron transport, which causes an energy crisis followed by apoptosis/necrosis. The depletion of ATP initiates an apoptotic cell death mechanism [61]. Methamphetamine-induced toxicity is thought to occur through a process

that resembles apoptosis. This is evidenced by studies that show that p53 transcription factor, which is associated with the induction of cell death, accumulates following the administration of methamphetamine [43]. The damage to the nigral cell bodies and striatal terminals observed in methamphetamine users is indicative of all of the above discussed toxic mechanisms. Oxidative stress, inhibition of electron transport chain, excitotoxicity, inflammation and apoptosis all play a significant role in methamphetamine-induced toxicity. These mechanisms are also indicated in Parkinson's disease [46, 51]. Therefore, blocking the disruption of these mechanisms could prevent cell damage and death.

Methamphetamine toxicity: relevance to Parkinson's disease

Parkinson's disease is the most common of all neurodegenerative movement disorders [96]. It is a common cause of disability in the elderly, with approximately 800 of 100,000 individuals over age 65 affected [89]. Parkinson's disease causes a significant economic impact. It is estimated that the medical costs alone amount to approximately 25 billion dollars per year [21]. Investigation of the neurotoxicity of methamphetamine, its role in dopamine depletion, and implications for Parkinson's disease could aid in closing the gap in understanding the disease, which could lead to proactive strategies to combat it [50, 48]. The abuse of drugs, such as methamphetamine, also has a significant economic impact worldwide. The cost of drug abuse around the world is estimated at approximately one trillion dollars per year [12, 76]. A better understanding of the mechanistic properties of this drug could also aid in strategies to combat addiction. Therefore, the investigation of these properties has a two-fold beneficial effect for the world's economy.

The risk of Parkinson's disease increases with age, which poses a significant problem with today's prolonged life span. In Parkinson's disease, nigrostriatal dopaminergic neurons undergo selective neuronal degeneration, leading to a shortage or depletion of dopamine in the striatum [13, 44]. Neurons in the striatum require dopamine to effectively control movement. Thus, the neurodegeneration in Parkinson's disease causes motor deficits such as slowness in initiation and execution of voluntary movements, increased muscle tone, increased resistance to movement, shuffling of feet, stooped posture and equilibrium and righting reflex. These deficits are evidenced by various motor symptoms including resting tremors, bradykinesia, muscular rigidity, and abnormalities in posture and gait.

Parkinson's disease is a progressive disorder and complete immobility typically occurs, despite treatment [58, 67, 91]. The specific cause of Parkinson's disease is unknown, but numerous studies have shown that age, genetics and environmental factors all contribute to the disease [39, 67, 80, 91]. Parkinson's disease can be either a sporadic or a familial form of disease. The genes that can cause the familial form of Parkinson's disease are α-synuclein, parkin, DJ-1, PINK-1, PTN, and LRRK2. Environmental toxins have repeatedly been shown to contribute to the development of Parkinson's disease [10, 20, 23, 80, 92, 110]. Studies have implicated exposure to toxins, such as the synthetic heroin compound l-methyl-4-phenyltetrahydropyridine (MPTP) [10, 20, 23, 92], herbicides/pesticides [23] and the highly abused drug methamphetamine [8], as a contributor to the development of Parkinson's disease. It is well known that a significant degree of striatal dopamine depletion is produced by such neurotoxins [24]. This fact makes toxins useful in the creation of animal models to study the different aspects of Parkinson's disease. Levodopa with carbidopa, dopamine agonists, and monoamine oxidase inhibitors are the current major class of drugs used for the therapeutic treatment of Parkinson's disease. There are also few surgical approaches used in current treatment. With no proven neurorestorative or neuroprotective treatment strategies for this disease, animal models are essential to discovering treatments that are not merely symptomatic and to lowering the mortality rate of this disease [21].

Major markers evidenced in Parkinson's disease are nigral neuronal loss and reduced tyrosine hydroxylase activity, leading to dopamine depletion in the striatum. Similarly, in humans, examination of *post-mortem* brain tissue from methamphetamine users has shown a significant decrease in striatal dopamine and dopamine transporter density [113]. Interestingly, repeated administration of methamphetamine also caused neurotoxicity in both rodents and non-human primates [41, 116]. Methamphetamine treatment depletes dopamine as well as its metabolite, 3,4-

dihydroxyphenylacetic acid (DOPAC), in the striatum [8]. It has been further shown that repeated administration of methamphetamine reduces DAT binding affinity and, in extreme cases, causes apoptosis [12, 19, 57]. Toxicological studies on the brain tissue of human methamphetamine users have shown long-term and possibly irreversible damage to dopaminergic neurons and loss of striatal dopamine transporters even after three years of abstinence from the drug [12]. Researchers have found dopaminergic toxicity in mice after a single dose of methamphetamine (25 mg/kg) [42] or after multiple doses of methamphetamine varying from 2.5 to 10 mg/kg given at two-hour intervals [15, 78, 97]. After such doses of methamphetamine, there was a long- lasting decrease in nigrostriatal dopamine similar to that seen in Parkinson's disease [98].

Although the exact mechanism of the neurotoxicity caused by methamphetamine use is unclear, oxidative stress and mitochondrial dysfunction, as well as NMDA receptor-mediated excitotoxicity and neuroinflammation are all mechanisms commonly implicated in this neurotoxicity. In addition, the long-lasting damage to striatal neurons mimics the scenario seen in the neurodegenerative process in Parkinson's disease. Hence, these features make the methamphetamine animal model a valid tool for exploring the neuropathological features of Parkinson's disease [34, 57, 62, 63, 86, 105].

Novel neuroprotective approaches

In summary, the previous sections provide literature support for the neurotoxic effects of methamphetamine and discuss the mechanisms implicated in causing damage to dopaminergic cells. Methamphetamine use significantly increases the risk for nigrostriatal neurodegeneration. The mechanistic similarity of methamphetamine toxicity to the dopaminergic neurodegeneration seen in Parkinson's disease indicates the usefulness of this model for testing pharmacological agents for neuroprotective properties against this neurodegeneration. The literature supports the idea that in Parkinson's disease, oxidative stress and mitochondrial dysfunction are primary mediators of excitotoxicity, neuroinflammation and apoptosis [74]. Thus, if a pharmacological agent blocks these neurotoxic mechanisms, it could provide protection from the resulting neurodegeneration.

Antioxidants

Oxidative stress and mitochondrial dysfunction play a key role in neurodegeneration. Research on coenzyme Q_{10} (antioxidant and mitochondrial energy enhancer) and other antioxidants has shown that they could possibly be neuroprotective against the neurodegeneration found in Parkinson's disease as well as other neurodegenerative diseases [95]. Coenzyme Q_{10} has been shown to provide neuroprotection against both MPTP [2] and rotenone [93]. Also, clinical studies have shown that Q_{10} can provide some protection for the nigrostriatal dopaminergic system and slow the progressive disability of Parkinson's disease [95]. In addition, free radical scavengers have been shown to provide neuroprotection against toxin-induced oxidative stress such as that caused by MPTP and methamphetamine [53, 73]. Ramelteon is a novel melatonin receptor agonist that is used to treat insomnia. Melatonin is known to have neuroprotective effects such as antioxidant and antiapoptotic properties. If ramelteon possesses the same capacity for free radical scavenging as melatonin, it could provide much needed neuroprotection against oxidative stress that leads to neurodegeneration and reduce the oxidative damage seen in Parkinson's disease.

Ramelteon is an orally active sleep agent (for insomnia) and a hypnotic substance that is commercially available as rozerem from Takeda Pharmaceuticals, North America [100, 101]. Ramelteon is approved by the FDA for long-term use in the treatment of insomnia and is the first in a new class of sleep agents that selectively binds to MT_1 and MT_2 receptors [79], which is believed to contribute to its sleep-promoting properties as these receptors are thought to be involved in the maintenance of the circadian rhythm underlying the normal sleep-wake cycle [72]. The significance of ramelteon's lack of affinity for the MT_3 receptor is not clear; however, the MT_3 receptor appears almost exclusively in the gut and does not appear to have a relationship with sleep or wakefulness [28, 115]. Unlike other hypnotic drugs such as zolpidem, eszopiclone, and zaleplon, ramelteon does not show appreciable binding to $GABA_A$ receptors. These receptors are associated with the anxiolytic, myorelaxant, and amnesic effects of other sleep agents [111]. Hence, ramelteon has not been shown to produce dependence and potential for abuse. Furthermore, the withdrawal and rebound insomnia that is

typical with other GABA modulators is not present with ramelteon. It is currently the only non-scheduled prescription drug for the treatment of insomnia available in the United States [54, 101].

Ramelteon possesses structural similarities with melatonin and, therefore, has similar physiological effects. It is possible that some of these shared effects are the antioxidant and antiapoptotic properties previously shown in melatonin research. Melatonin is an antioxidant that easily crosses cell membranes and the blood-brain barrier [39, 102]. Research has established that melatonin is a direct scavenger of reactive oxygen species (ROS), such as OH, O_2^-, and NO [81]. It has also been found to be effective in protecting against brain injury caused by ROS release in experimental hypoxic brain damage in newborn rats [74, 107]. In animal models, melatonin has been demonstrated to prevent some carcinogens from damaging DNA, stopping the mechanism by which they cause cancer [52]. Its antioxidant activity may reduce the neuronal damage found in several neurodegenerative disorders, including Parkinson's disease [77]. Whether ramelteon has functional similarities with melatonin besides induction of sleep has not been fully studied. However, besides the primary function of regulating the sleep cycle, both may exert powerful antioxidant activity [103]. If ramelteon possesses the same free radical scavenging properties and anti-apoptotic effect as melatonin [83], then it could prove to be a neuroprotective drug and reduce the oxidative damage found in Parkinson's disease.

NMDA receptor antagonists

Since NMDA receptors are especially harmful factors in excitotoxicity, antagonists of the receptors show promise for the treatment of conditions that involve excitotoxicity, including traumatic brain injury, stroke, and neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease and Huntington's disease [65]. Research has shown that excitotoxic effects of glutamic acid can be blocked by NMDA receptor antagonists [17]. In experiments using MPTP, an NMDA receptor antagonist (memantine) protected rats from the toxic effects of this toxin [106]. Memantine is proposed to counteract cellular damage due to pathological activation of NMDA receptors by glutamate and has been approved in Europe as the first treatment of its type for moderately severe to severe Alzheimer's disease [26]. Further studies have shown that antagonists of mGluR1 prevented NMDA-induced neurotoxicity. A selective mGluR1 antagonist, (RS)-1-aminoindan-1,5-dicarboxylic acid (AIDA), protected against MPTP-induced injury of dopaminergic nigral cells [1]. In addition, the mGluR5 antagonist, 2-methyl-6-(phenylethynyl)pyridine (MPEP), prevented the degeneration of dopaminergic neurones induced by methamphetamine in rats [35].

Amantadine is sold commercially as amantadine hydrochloride, under the name symmetrel, for use both as an antiviral and an antiparkinsonian drug [88]. Amantadine was approved by the FDA in October 1966 as a prophylactic agent against Asian influenza and eventually received approval for the treatment of influenzavirus A in adults [68, 69]. In terms of the mechanism of its antiviral properties, amantadine interferes with the viral protein M2 (an ion channel), which is required for the viral particle to become "uncoated" once it is taken inside the cell by endocytosis. In 1969, the drug was also accidently discovered to help reduce the symptoms of Parkinson's disease. The mechanisms for its antiviral and antiparkinsonian effects seem to be unrelated. The mechanism of its antiparkinsonian effect is poorly understood. The drug appears to induce the release of dopamine from the nerve endings of the brain cells, together with stimulation of the norepinephrine response. Furthermore, it appears to be a weak NMDA receptor antagonist and an anticholinergic [7]. As an antiparkinsonian, it can be used as monotherapy or together with levodopa to treat levodopa-related motor fluctuations, shorten levodopa's duration of clinical effect, and treat levodopa-related dyskinesias, such as choreiform movements associated with long-term levodopa use [88].

Amantadine also has several off-label uses and is frequently used to treat the characteristic fatigue often experienced by patients with multiple sclerosis [18]. Additionally, there have been anecdotal reports that low-dose amantadine has been successfully used to treat ADHD [38]. Amantadine has also been shown to relieve selective serotonin reuptake inhibitors-induced sexual dysfunction [4, 55, 94]. It is amantadine's effectiveness as an NMDA receptor antagonist that led to its inclusion in this study as possibly neuroprotective. As previously mentioned, because NMDA receptors are especially harmful factors in excitotoxicity, antagonists of the receptors show promise for the treat-

ment of conditions that involve excitotoxicity [65]. Excitotoxicity is commonly seen in Parkinson's disease and the defective mitochondrial energy metabolism found in Parkinson's disease patients may predispose them to excessive glutamate- evoked calcium influx. This could cause toxicity to the nigral neuronal cells [5, 6]. MPTP-induced parkinsonism is attenuated by a blockade of NMDA receptors [60, 75]. Amantadine is the only NMDA receptor antagonist that is actively used to treat Parkinson's disease. If it is proved to be neuroprotective against methamphetamine-induced toxicity in addition to its well-established therapeutic use, then it would be cost-effective as well as ground-breaking.

Anti-inflammatory agents

Salicylic acid belongs to a class of drugs known as analgesics or antipyretics. It is a metabolite produced in the body following ingestion of aspirin, acetylsalicylic acid [40]. Aspirin was the first member of the class of drugs known as non-steroidal anti-inflammatory drugs (NSAIDs) to be discovered; NSAIDS all have similar effects, and most inhibit the enzyme cyclooxygenase as their mechanism of action [112]. Aspirin suppresses the production of prostaglandins and thromboxanes. Prostaglandins are local hormones produced in the body that have diverse effects, including the transmission of pain information to the brain, modulation of the hypothalamic thermostat, and inflammation. Thromboxanes are responsible for the aggregation of platelets that form blood clots. Aspirin's ability to suppress the production of prostaglandins and thromboxanes is due to its irreversible inactivation of the COX enzyme. COX is required for prostaglandin and thromboxane synthesis. Aspirin acts as an acetylating agent through which an acetyl group is covalently attached to a serine residue in the active site of the COX enzyme. Thus, aspirin differs from other NSAIDs, such as ibuprofen, which are reversible inhibitors. There are at least two different types of cyclooxygenase: COX-1 and COX-2. Aspirin irreversibly inhibits COX-1 and modifies the enzymatic activity of COX-2. Normally, COX-2 produces prostanoids, most of which are proinflammatory. Aspirin-modified COX-2 produces lipoxins, most of which are anti-inflammatory [108, 109]. The administration of methamphetamine is associated with the induction of COX, which causes a neuroinflammatory process that results in deleterious events in the cell [117]. Since non-steroidal anti-inflammatory drugs have shown neuroprotection against other neurotoxins [104], this supports the use of anti-inflammatory therapeutic agents for reducing neurodegeneration. Salicylic acid and ketoprofen have been shown to provide neuroprotection against MPTP-induced neurotoxicity [3, 53, 73]. Thus, these agents could play a much needed neuroprotective role in numerous other neurodegenerative disorders.

Other therapies

There are other relevant therapeutic models in the methamphetamine model of Parkinson's disease. Dopamine receptor agonists are currently in use as anti-parkinsonian treatments. Pramipexole, a dopamine D_2/D_3 receptor agonist, has been shown to provide neuroprotection against methamphetamine-induced degeneration of nigrostriatal neurons [36]. Also, adenosine receptor agonists are of interest due to evidence that the microglial activation by methamphetamine is related to the downregulation of the adenosine glial transporter [29]. Other treatments of interest include selenium, which has shown antioxidant properties [56], and apomorphine, which has shown free radical scavenging properties [33].

Conclusion

Specific animal models have been developed to obtain insight into the selective loss of nigral dopaminergic neurons. These models are designed to reproduce the clinical and pathological features of Parkinson's disease, and can be quite helpful in dissecting the many different molecular and biochemical pathways. As such, the methamphetamine animal model can facilitate a greater understanding of the neurodegeneration in the nigrostriatal system associated with Parkinson's disease, and can be used to investigate pharmacological agents to determine what, if any, neuroprotective or neurorestorative effects they ex-

hibit. Such investigations may lead to the development of much needed novel therapeutic agents and even to a proactive treatment strategy for Parkinson's disease. A more complete understanding of the progressive and selective loss of nigrostriatal dopaminergic neurons that occurs in aging and in Parkinson's disease could advance treatment. The discovery of novel pharmacological agents that provide neuroprotection in the substantia nigra against oxidative stress, scavenge hydroxyl radicals or upregulate antioxidant defense enzymes or the identification of a therapy that protects dopaminergic neurons from apoptosis may improve the duration and quality of life of all patients with Parkinson's disease.

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