

Perspective

Do Preclinical Findings of Methamphetamine-Induced Motor Abnormalities Translate to an Observable Clinical Phenotype?

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This review summarizes the preclinical literature of the effects of methamphetamine (MA) on subcortical dopaminergic and GABAergic mechanisms underlying motor behavior with the goal of elucidating the clinical presentation of human MA-induced movement disorders. Acute and chronic MA exposure in laboratory animal can lead to a variety of motor dysfunctions including increased locomotor activity, stereotypies, diminished or enhanced response times, and parkinsonian-like features. With the exception of psychomotor impairment and hyperkinesia, MA-induced movement disorders are not well documented in humans. This review attempts to draw parallels between the animal and human changes in basal ganglia neurochemistry associated with MA exposure and offers explanations for why a parkinsonian phenotype is not apparent among individuals who use and abuse MA. Significant differences in the expression of neurotoxicity and presence of multiple environmental and pharmacologic confounds may account for the lack of a parkinsonian phenotype in humans despite evidence of altered dopamine function.

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INTRODUCTION AND OVERVIEW

The goal of this review paper is to summarize the preclinical and clinical evidence for subcortical mechanisms underlying the motor abnormalities associated with methamphetamine (MA) abuse. The focus of this review will be on basal ganglia mechanisms because of the powerful neurochemical interactions that occur between MA and dopamine (Ricaurte *et al*, 1980, 1984; O'Dell *et al*, 1993; Volkow *et al*, 1999), GABA (Bustamante *et al*, 2002; Kamata and Kameyama, 1986), and glutamate (GLU) (Sonsalla *et al*, 1989; Nash and Yamamoto, 1992; Abekawa *et al*, 1994), three important neurotransmitters present throughout the basal ganglia. Recent findings indicate that the motor consequences of even brief exposures to psychostimulants can persist long after the stimulant is discontinued (Balogh *et al*, 2004). The state of knowledge is quite advanced with regard to the effects of MA exposure on brain neurochemistry. However, our understanding of how these changes impact motor behavior in the living animal is less sophisticated particularly with regard to MA-induced motor dysfunction in humans. In this paper, we review selected

research on the anatomic and neurochemical bases for MA-induced motor abnormalities in laboratory animals. We then discuss whether these mechanisms are sufficient to produce movement disorders in humans who abuse MA and cite similarities and differences between MA-induced motor abnormalities in laboratory animals and humans. Limitations in the clinical literature are discussed and recommendations for further research are presented.

NEUROANATOMY AND CHEMISTRY OF THE SUBCORTICAL MOTOR SYSTEM

Progress has been made in identifying the underlying neural circuitry involved in extrapyramidal motor function in humans and primates. Over the past 20 years, the brain systems involved in extrapyramidal motor function have been elucidated to an important degree. The regions involved form a circuit, through which information is passed from the cortex, to the striatum, then to the globus pallidus, to the thalamus, and back to the cortex (Albin *et al*, 1989; Alexander *et al*, 1990; DeLong, 1990). The cortico-striato-pallido-thalamic (CSPT) circuits are the best known and most thoroughly investigated groups of circuits in the brain (Lichter and Cummings, 2001; Bradshaw, 2001). Figure 1 shows a diagram of the CSPT motor circuit. The CSPT motor circuit consists of direct and indirect motor loops involving the basal ganglia. The direct loop consists of a circuit involving the cortex, striatum, internal segment of the globus pallidus/substantia nigra pars reticulata

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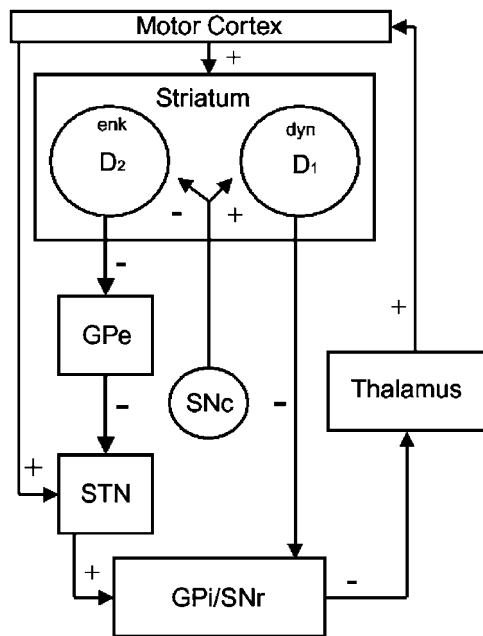


Figure 1 Diagram of the cortico-striato-pallido-thalamic motor circuit showing inhibitory (–) and excitatory (+) pathways. Abbreviations: D1—dopamine D1 receptor; D2—dopamine D2 receptor; dyn—dynorphin; enk—enkephalin; GPe—external segment of the globus pallidus; GPi—internal segment of the globus pallidus; SNc—substantia nigra pars compacta; SNr—substantia nigra pars reticulata; STN—subthalamic nucleus.

(GPi/SNr) complex, thalamus and cortex, in which dopamine input from the substantia nigra pars compacta (SNc) is excitatory upon GABAergic and cholinergic striatal neurons. The indirect loop consists of a more complex circuit, involving the cortex, striatum, external segment of the globus pallidus (GPe), the subthalamic nucleus (STN), GPi/SNr complex, thalamus, and cortex, in which dopamine from the SNc is inhibitory to GABAergic neurons of the striatum.

Localizing the neuronal circuits involved in parkinsonism has been the focus of animal and human research for over two decades. Primate models of basal ganglia disorders demonstrate that parkinsonian bradykinesia results from disruptions of normal inhibitory striatal projections to the internal segment of the globus pallidus (Albin *et al*, 1989; Alexander *et al*, 1990; Delong, 1990). Excessive inhibition of outflow projections from GPi to the thalamus thus reduces the thalamocortical excitation and reduced cortical excitation. This in turn would lead to a reduction (hypokinesia) or slowing (bradykinesia) of movement. Horak and Anderson (1984) and Mink and Thatch (1993) observed that monkeys with lesions causing increased activity within the GPi exhibited significant motor slowing. The therapeutic effects of surgical disruption of the output of the GPi in Parkinson disease are also consistent with this model (Pfann *et al*, 1998; Alkhani and Lozano, 2001; Lozano and Lang, 2001; Dostrovsky *et al*, 2002).

Neuroanatomical and neurochemical bases for dyskinesia have been elucidated through studies of animal lesions (Alexander *et al*, 1990; Delong, 1990) and drug-induced

dyskinesia in humans (Pahl *et al*, 1995; Rascol *et al*, 1998; Brooks *et al*, 2000; Henry *et al*, 2003). Dyskinesia can result from a loss of striatopallidal GABAergic inhibitory outflow to thalamic neurons causing increased thalamo-cortical excitation (Albin *et al*, 1989; Alexander *et al*, 1990; Delong, 1990). This model assumes strong interactions between dopamine (at the level of the striatum), enkephalin (mediating GABAergic activity), inhibitory GABA (within the globus pallidus), and excitatory GLU (at the level of the subthalamic nucleus).

MA-INDUCED ALTERATIONS IN NEUROCHEMISTRY

Preclinical Studies

Several mechanisms account for the alterations in striatal neurochemistry in rats following exposure to MA including postsynaptic elevation in nigrostriatal monoamine levels, increased striatal dopamine turnover, neurotoxic effects on striatal cells via both apoptotic and neurotoxic mechanisms, and reactive gliosis or an inflammation response.

MA exerts powerful effects on several neurochemical systems throughout the brain, including dopamine (Ricaurte *et al*, 1980, 1984; O'Dell *et al*, 1993), GABA (Kamata and Kameyama, 1986; Burrows and Meshul, 1999; Bustamante *et al*, 2002), and GLU (Sonsalla *et al*, 1989; Nash and Yamamoto, 1992; Abekawa *et al*, 1994; Burrows and Meshul, 1999). MA is a highly lipophilic monoamine that is capable of entering presynaptic vesicles and competing for resident monoamines causing excessive release postsynaptically (Kuczenski, 1983). Both acute and prolonged MA exposures can elevate nigrostriatal dopamine postsynaptically (Kita *et al*, 2003; Cadet *et al*, 2003). Acute MA exposure can increase dopamine turnover in the caudate nucleus, as measured by the ratio of DOPAC (3,4-dihydroxyphenylacetic acid) to HVA (homovanillic acid, both intermediate metabolites of dopamine) relative to dopamine (Pereira *et al*, 2002). Bustamante *et al* (2002) reported changes in monoamines and peptides during an acute MA binge in the basal ganglia. Using *in vivo* microdialysis, they found a 10 times increase in nigral dopamine and a 40 times increase in the neostriatum in rodents. Level of dynorphin B, a cotransmitter released with excitation, was doubled in the neostriatum and substantia nigra. Prolonged exposure to MA has neurotoxic effects on striatal cells via both apoptotic (Cadet *et al*, 2003) and neurotoxic mechanisms (Davidson *et al*, 2001) associated with a marked decrease in tyrosine hydroxylase activity, dopamine, and dopamine transporter (DAT) binding sites in the striatum (Kogan *et al*, 1976; Gibb *et al*, 1990). The acute neurochemical effects of MA appear to be mediated by a precipitous rise in postsynaptic dopamine, with relative activation of the direct circuit via GLU and altered cotransmitter release. Chronic administration of these sympathomimetics appears to cause a relative decrease in the neural catecholamine activity at baseline as measured by dopamine receptor and ligand populations.

Glial cell activation is an important end point marking neurotoxicity in MA-exposed animals. Chronic exposure to MA induces reactive gliosis in the striatum (Escubedo *et al*, 1998; Miller *et al*, 2000; Guilarte *et al*, 2003) as well as other brain regions including the cerebellum and hippocampus

(Escubedo *et al*, 1998). Miller *et al* (2000) evaluated striatal levels of glial fibrillary acidic protein (GFAP) as a marker of dopamine nerve terminal degeneration in the mouse striatum. Exposure to neurotoxic dosages of MA resulted in persistent decreases in striatal dopamine and its metabolites (DOPAC and HVA) as well as a 300–400% increase in GFAP. These alterations were observed to a much lesser extent in younger (2–3 months) compared to older (12 months) animals. Work by Thomas *et al* (2004) and Thomas and Kuhn (2005) indicates that MA-induced microglial activation may be attenuated in animals previously treated with MA, suggesting that animals can develop tolerance to the neurotoxic and degenerative effects of MA.

Studies of abstinence have enhanced our understanding of MA influence on basal ganglia neurochemistry. Friedman *et al* (1998) exposed 60-day-old rats to neurotoxic levels of MA and investigated monoamine depletion in groups of animals killed 48, 139, and 237 days later. There were significant depletions in post-mortem monoamine tissue at 48 days but not 139 and 237 days in dopamine, serotonin, and their metabolites. 5-HT within the medial prefrontal cortex, caudate, and hippocampus were reduced to 30% of control with recovery in the medial prefrontal cortex and caudate to 70% of control following long-term abstinence. Additionally, caudate dopamine reduced to 30% of control levels and showed recovery to 80% following long-term abstinence. Melega *et al* (1997) reported decreases in presynaptic striatal dopamine of 60% 1–2 weeks following MA exposure with partial recovery when measured 6 and 12 weeks after acute MA exposure. Cass and Manning (1999) utilized *in vivo* microdialysis studies in rats pretreated with acute MA doses and demonstrated that amphetamine and potassium-evoked outflow of dopamine in the striatum would fully recover at 12 months. These data suggest that postsynaptic response to dopamine can recover at 12 months abstinence.

Dopamine is not the only neurotransmitter affected by MA. Bustamante *et al* (2002) observed chronic changes after repeated acute MA binges in rats including a decreased release of dopamine in both the neostriatum and substantia nigra and increases in GLU and GABA levels. The authors concluded that repeated MA administration might alter dopamine homeostasis and perhaps overstimulation of striatal GLU NMDA receptors. Alterations in GABA and GLU are likely to be important to the behavioral changes observed following MA exposure in animals. MA-induced alterations in nigrostriatal dopamine can influence GABAergic and glutamatergic transmission downstream and produce a variety of motor disturbances. Floran *et al* (1977) reported that acute MA administration in rats decreased GABA levels via their direct interaction within the striatal dopamine subsystem. Burrows and Meshul (1999) reported striatal and pallidal decreases in GABA immunoreactivity following 1 week of MA exposure; however, GABAergic immunoreactivity increased following prolonged exposure for up to 4 weeks. Prolonged exposure to MA altered presynaptic GABA immunolabeling and increased GLU terminal size in both the striatum and globus pallidus. The authors concluded that these dynamic changes within the striatopallidal pathway were similar to those found following nigrostriatal lesions in animals in which

dopamine loss alters GABAergic striatopallidal neurotransmission.

There are reports demonstrating sparing of GABAergic systems in rats exposed to MA (Chapman *et al*, 2001). Kaiya *et al* (1983) found that 16 days of MA administration did not change GABA levels in the striatum, whereas Kamata and Kameyama (1986) reported that 6 days of MA exposure, twice daily, increased striatonigral GABA activity. Discrepancies in how MA affects GABA levels may be explained by differences in exposure duration and/or where GABA levels are measured. Nonetheless, it is likely that MA decreases striatal GABA neurotransmission acutely.

Change in temperature regulation has been shown to mediate the neurotoxic effects of MA, with higher body temperatures facilitating neurotoxicity (Cadet *et al*, 2003). In rodents, holding the body temperature constant can markedly reduce the toxic effects of MA on the basal ganglia (Burrows and Meshul, 1999). Bowyer *et al* (1994) and others (Fukumura *et al*, 1998) have shown that MA-induced hyperthermia is correlated with neurotransmitter reduction in the adult, but not in the developing rat. Cappon *et al* (1997) argued that induction of hyperthermia is a requisite for the expression of MA-induced striatal dopamine neurotoxicity. There is some evidence that DAT may play an important role in the expression of MA-induced hyperthermia and neurotoxicity (Xie *et al*, 2000; Broening *et al*, 2005). Broening *et al* (2005) found that coadministration of dopamine D₁ and D₂ receptor antagonists attenuated both the MA-induced reduction in striatal dopamine and hyperthermia in rats. However, when animals were subjected to ambient temperatures known to facilitate hyperthermia, only the D₂ receptor antagonist continued to provide protection. The authors concluded that D₂ receptor antagonist eticlopride blocked striatal DAT activity and inhibited presynaptic DA release. Thus, the mechanism thought to underlie MA-induced hyperthermia and dopamine neurotoxicity may involve D₂ receptor-mediated upregulation of DAT activity.

In summary, MA alters both excitatory and inhibitory neurotransmitter systems in the brain. Its predominant acute effect is to increase nigrostriatal dopamine. Elevated nigrostriatal dopamine would manifest as increased locomotor activity and stereotypy in animals and hyperkinesia in humans. Elevated nigrostriatal dopamine, especially involving the D₂ receptor system, leads to a decrease in striatopallidal GABA level. This pathophysiology can produce a loss of inhibitory regulation and hyperkinetic movements. It has been proposed that prolonged or chronic MA exposure may have neurotoxic effects on striatal dopamine neurons manifesting as reduced locomotor behavior or parkinsonism. These neurotoxic effects manifest anatomically by reactive gliosis and decreases in evoked dopamine metabolites. Additionally, environmental changes, such as hyperthermia, may play an important role in MA neurotoxicity whether direct or indirect. The ameliorative effects of abstinence are largely unknown. There is literature to support partial recovery in monoamine levels (Friedman *et al*, 1998; Melega *et al*, 1997) in rats when measured 6–9 months following acute exposure to MA. Yet, Cass and Manning (1999) reported full recovery in potassium-evoked outflow of dopamine in the striatum 12 months after acute MA exposure, suggesting a possible

role of sensitization as a homeostatic mechanism for recovery after a neurotoxic MA insult. A study in primates indicated persistent dopamine and serotonin depletion up to 4 years following high-dose MA treatment (Woolverton *et al*, 1989). It has been speculated that age of the animal may be an important determinant in how much recovery of neurotransmitter function is observed with long-term abstinence (Seiden *et al*, 1993) with older animals showing less recovery.

Clinical Studies

Functional neuroimaging approaches are beginning to shed light on the effects of MA exposure on striatal neurochemistry in humans. Of particular relevance to this review are the positron emission tomography (PET) studies of striatal DAT density (Volkow *et al*, 1999, 2001b), dopamine receptor occupancy (Volkow *et al*, 2001a), and regional brain glucose metabolism (Volkow *et al*, 2001c; Wang *et al*, 2004). PET studies of DAT availability implicate the striatum in both psychomotor and cognitive disturbances associated with MA abuse. PET studies have shown up to a 25% reduction in DAT in the caudate and putamen among MA users (McCann *et al*, 1998; Volkow *et al*, 2001b). Findings indicate that the striatum may be more vulnerable to the neurotoxic effects of MA and may be slower to recover following abstinence than the thalamus (Wang *et al*, 2004).

Ernst *et al* (2000) using proton magnetic resonance spectroscopy reported a 5% decrease in *N*-acetylaspartate (a marker of long-term neuronal damage) in the basal ganglia and an 11–13% increase in myo-inositol and choline-containing compounds (markers of glial abnormality) in frontal gray matter in abstinent MA users. The decreased *N*-acetylaspartate and increased myo-inositol suggest glial proliferation secondary to neuronal damage. It is interesting that neuronal damage was present in subjects abstinent for as long as 21 months. While these findings are generally consistent with the preclinical findings on neuronal damage, they do not provide the necessary detail to help localize the damage to a particular basal ganglia pathway or to identify region-specific vulnerabilities to chronic MA exposure in humans. However, Chang *et al* (2005) recently reported both striatal and pallidal enlargement in abstinent MA abusers based on structural MRI. Their MA abusers showed larger globus pallidus (9.6%) and putamen (9.9%) volumes compared to age and gender comparable controls. While the specific etiology of the structural enlargement is uncertain, the authors attributed their findings to MA-induced striatal injury leading to inflammation and reactive gliosis. These studies contribute to the general notion that long-term MA exposure in humans and rodents leads to striatal and pallidal injury manifested by tissue inflammation and gliosis.

MOTOR DYSFUNCTION FOLLOWING MA

Preclinical Studies

In the mid-1970s Baker *et al* (1976) reported that intracaudate injections of *D*-amphetamine led to motor hyperactivity in cats. Injection of *D*-amphetamine initiated

tremorous paw movements while administration of dopamine into the striatum attenuated the response. Studies have since highlighted the fact that amphetamines, including MA, produce hyperkinetic states in animals characterized by stereotypies (Wallace *et al*, 1999; Kuczenski and Segal, 2001), increased locomotor responses (Riviere *et al*, 1999; Szumlinski *et al*, 2000), and prolonged dose-dependent reaction during a choice RT task (Mishima *et al*, 2002; Sabol *et al*, 2003).

In general, these conditions are dose dependent (Riviere *et al*, 1999) and occur within a few days following MA injection (Timar *et al*, 2003). Segal and Kuczenski (1997) found that rats exposed to escalating high-dose binges exhibited increased locomotor activity compared to rats exposed to intermittent dosing of MA. In their study, stereotypies were related to cumulative dose rather than dosing schedule. Additional support for the importance of dopamine in the development of MA-induced motor abnormalities comes from studies of dopamine knockout mice. These animals exhibit a generalized state of catatonia and insensitivity of the response to MA (Nishii *et al*, 1998).

Consideration has been given to the selected effects of MA on dopamine receptor subpopulations and their respective behavioral attributes. G-protein coupled dopamine receptors have been classified into two families based on their effects on adenylate cyclase. Members of the dopamine D1 receptor family stimulate adenylate cyclase when stimulated, whereas members of the D2 family inhibit or have no effect on adenylate cyclase. D2 receptors are 2 to 3 times more sensitive than D1 receptors to dopamine (Missale *et al*, 1998). The animal literature suggests that MA alters both D1 and D2 dopamine receptor functions; however, there is some evidence that the effects on the D1 and D2 striatopallidal pathways may differ.

With regard to specific changes to the dopamine D1 (direct striatopallidal) system, MA administration has been shown to increase expression of kappa opioid receptors in the striatum and to decrease dopamine D1 receptors Adams *et al* (2003) reported an increased dynorphin release in striatal patch division in rats following MA administration. Cadet *et al* (1998) found that MA decreases striatal D1 receptors. Studies of transgenic D1 knockout mice report diminished effects of psychostimulants on striatal neurons, particularly in the striosomal compartment (Moratalla *et al*, 1996). Two studies reported direct effects of kappa receptor agonists on MA-induced dopamine release. Kuribara and Uchihashi (1994) found that coadministration of a kappa receptor agonist reduced striatal dopamine levels and inhibited MA-induced locomotor activity. Similarly, kappa receptor agonists potentiated striatal dopamine loss (Johnson-Davis *et al*, 2003) and can normalize the increased behavioral sensitivity induced by MA administration (Toyoshi *et al*, 1996). Additional evidence implicating a striatal D1 receptor mechanism stems from the work of Hanson *et al* (2002), who found increased expression of substance P in the substantia nigra following acute MA exposure that was blocked by a dopamine D1 receptor agonist.

While the evidence supporting a dopamine D1 mechanism for the behavioral consequences of MA is compelling, there is evidence to the contrary. For example, Gifford *et al* (2000) found that MA-induced striatal dopamine release

interfered with D2 but not D1 receptor tracer binding. It has been argued that this effect may be due to the dramatic decrease in sensitivity of the D1 receptor to dopamine following MA exposure rather than competition for receptor binding sites Schoffemeer *et al* (1994).

With regard to the specific changes to the dopamine D2 (indirect striatopallidal) system, MA administration has been shown to decrease D2 receptor binding affinity and increase expression of mu opioid receptors in the striatum. As noted above, Gifford *et al* (2000) found that MA-induced striatal dopamine release interfered with D2 receptor tracer binding. Doudet and Holden (2003) also reported that MA competed for the same D2 receptors as the dopamine antagonist, raclopride. Magendzo and Bustos (2003) demonstrated in rats that acute MA exposure resulted in increased transcription of mu opioid receptor and delta opioid receptor in the ventral tegmental area, which corresponded with an acute sensitization to MA. These results implicate the indirect striatopallidal pathway because of the colocalization of enkephalin (via the mu receptor) and GABA. MA-induced locomotor hyperactivity and stereotypy require normal D2 receptor function (Sano *et al*, 2003; Glickstein and Schmauss, 2004). This observation suggests that MA-related hyperkinesia may be less pronounced in aged compared with younger animals.

Preclinical studies show that MA administration can inhibit striatal activity via the dopamine D2 system and facilitate striatal activity via the dopamine D1 system. The results from studies of the opioid peptides and their receptors implicate the striatopallidal system in the pathogenesis of MA-induced behavioral changes. Specifically, increased sensitivity of the mu receptors to MA implicates the indirect striatopallidal system; whereas increased expression of kappa receptors implicates the direct striatopallidal system. The majority of the literature on dopamine receptor mechanisms in MA-induced behavioral change involved specific pharmacologic manipulations of the MA response. While these methods are useful for distinguishing the relevance of a particular dopamine subsystem (eg D1 or D2), these pharmacologic manipulations impose changes to neuronal systems that, even in the absence of MA coadministration, can alter motor behavior. In fact, opioid peptides have been employed for years as a potential adjunctive treatment for Parkinson's disease (Giuffra *et al*, 1993; Hille *et al*, 2001) and its complications (Henry and Brotchie, 1996). Nevertheless, this work has led to a greater understanding of the role of MA in behavioral disturbances regulated by the dopamine via the direct and indirect striatopallidal GABAergic pathways and their translation to movement disorders humans.

Clinical Studies

Preclinical findings from numerous studies utilizing a variety of approaches summarized above implicate both the direct and indirect striatopallidal pathways in the pathogenesis of MA-related movement disorders. MA has been shown to influence the dopamine regulatory systems in the basal ganglia both presynaptically (Gifford *et al*, 2000) and postsynaptically (Cadet *et al*, 1998), and can compromise both excitatory (via a D2 receptor mechanism)

and inhibitory (via a D1 receptor mechanism) functions (Toyoshi *et al*, 1996; Hanson *et al*, 2002). Contemporary models of basal ganglia function predict that dysfunctions within the nigrostriatal or striatopallidal circuits produce not only a failure to facilitate desired movements, but also failure to inhibit unwanted movements (Mink, 2003). The results from preclinical and clinical studies show that MA exposure increases nigrostriatal dopamine acutely, can decrease dopamine levels chronically, and can indirectly decrease GABAergic neurotransmission. In theory, disruption of excitatory or inhibitory striatopallidal neurotransmission by diminished or increased dopaminergic regulation would manifest as parkinsonism or hyperkinesia, respectively. Yet, the question remains: do the animal studies of MA-induced motor dysfunction elucidate the clinical manifestations in individuals who abuse MA? That is, is the nature of the movement disorder observed in MA abusers consistent with the mechanisms revealed by animal studies?

Clinically, MA-related movement disorders fall into three categories: acute reactions in the form of hyperkinesia, and persistent effects in the form of parkinsonism and psychomotor disturbances. Unfortunately, the current literature consists of very few systematic studies of MA-related movement disorders such that epidemiologic trends are not possible.

Our review of the literature turned up only three case reports on stimulant abuse and hyperkinetic movement disorders (Mattson and Calvery, 1968; Lundh and Tunving, 1981; Sperling and Horowitz, 1994) and only one of these pertained directly to MA (Sperling and Horowitz, 1994). This is surprising because of the overwhelming evidence from animal studies that MA exposure induced increased locomotor activity and stereotypies. In the human reports, the movement disorders were described as involuntary movements of the face, arms, legs, and trunk that often disappeared when engaged in voluntary movements. At times, the movements were rapid and ballistic and affected gait. In some individuals, the abnormal movements occurred during abstinence and persisted for a year or longer following discontinuation (Lundh and Tunving, 1981). Sperling and Horowitz (1994) described a 50-year-old male who presented to an emergency room with choreiform movements of the upper extremities, head, and neck following use of crystallized MA. The patient also exhibited mild psychosis and agitation leading the authors to conclude that the motor and behavioral symptoms were related to the central dopaminergic effects of MA. Symptoms returned to normal following a 7-day hospitalization.

Moszczyńska *et al* (2004) argued that parkinsonism may not be a feature of MA abuse in humans. Their argument was based on autopsy data showing greater reduction in dopamine levels in the caudate nucleus (61% reduction *vs* controls) compared with the putamen (50% reduction) in subjects testing positive for MA. The authors concluded that their MA subjects probably did not exhibit parkinsonism because dopamine levels had not dropped to levels sufficient to produce motor impairment; however, in the absence of clinical records supporting normal motor functions, the question of whether MA abuse is a risk factor for parkinsonism remains unanswered.

Among the four published studies on MA-induced reductions in dopamine neurotransmission in humans, none included information on the presence of parkinsonian motor signs (Wilson *et al*, 1996; Volkow *et al*, 2001a; McCann *et al*, 1998; Moszczynska *et al*, 2004). The PET imaging studies show losses of 25% for DAT and 10% for dopamine D2 receptors in the putamen (Volkow *et al*, 2001a; McCann *et al*, 1998). The post-mortem brain tissue studies show losses as high as 53% (Wilson *et al*, 1996; Moszczynska *et al*, 2004). However, these studies do not offer compelling evidence that MA abuse in humans necessarily produces parkinsonism. While it is likely that reductions in striatal dopamine levels may be insufficient to produce clinical signs of parkinsonism, without prevalence figures on clinical manifestations in MA abusers, this remains an open question.

MA has been shown to produce psychomotor disturbances based on the grooved pegboard test (Volkow *et al*, 2001d), trailmaking tests (Kalechstein *et al*, 2003; Simon *et al*, 2000), finger tapping (Toomey *et al*, 2003), and reaction time (Richards *et al*, 1993) tests. It is not clear, however, if these disturbances are secondary effects of subtle parkinsonism or hyperkinetic conditions or if they are independent of extrapyramidal disorders and reflect disturbances in planning, attention, or executive function. Chang *et al* (2002) suggested that psychomotor slowing in MA users might represent a subclinical form of parkinsonism.

Using PET, Volkow *et al* (2001d) observed a relationship between performance on the grooved pegboard and timed gait tasks and loss of DAT in the striatum in abstinent (12 months) MA abusers. Slower performance times were associated with lower levels of striatal DAT availability. Kalechstein *et al* (2003) reported that abstinent MA users had significantly poorer performance on measures of psychomotor speed (symbol digit modalities test) compared with controls. Subjects in this study were assessed at least 5 days following a positive urine test for MA. It is difficult to generalize the results from these two studies with regard to psychomotor impairment because of differences in the tasks used to assess psychomotor speed, lack of adequate control groups, and difference in duration of abstinence. Nonetheless, these findings indicate that psychomotor changes can persist beyond the early withdrawal phase following MA use.

Clinical studies suggest that the psychomotor disturbances associated with MA may not be due to basic motor processes, but rather involve higher-level motor processes such as set shifting, planning, and manipulation of information (Simon *et al*, 2000). This conclusion is consistent with the findings by Moszczynska *et al* (2004) that the neurotoxic effects of prolonged exposure to MA are more pronounced in the cognitive areas of the striatum (ie caudate) than the pure motor areas (ie putamen).

Toomey *et al* (2003) evaluated neuropsychological performance in 50 twin pairs. Subjects were selected for study because one member used stimulants weekly for at least 1 year and the twin sibling never used stimulants. Amphetamines were reported to be the drug of abuse on 40 of the 50 twin pairs. Subjects reported abstinence of at least 1 year prior to participating in the study. Several psychomotor tests including trailmaking test, grooved

pegboard test, and finger tapping were part of their comprehensive battery. The investigators found significantly poorer performance among the stimulant abusers compared with the nonabusing siblings on the trailmaking test (part A), grooved pegboard test, and finger-tapping test. These results confirm the presence of long-term residual deficits in psychomotor function associated with amphetamine abuse.

DO PRECLINICAL STUDIES OF MA-INDUCED MOTOR ABNORMALITIES TRANSLATE TO AN OBSERVABLE CLINICAL PHENOTYPE?

In humans, MA abuse has been shown to induce hyperkinetic movement disorders such as chorea and tics and there are several reports of impaired psychomotor performance. However, we could find no reports of clinically apparent parkinsonism induced by MA exposure. This suggests that while prolonged exposure to MA can produce alterations in striatal dopamine physiology in humans, these changes do not always lead to an observable parkinsonian phenotype. There are several explanations for this. It may be argued that parkinsonian symptoms are too subtle to be readily observed and that sensitive measurement tools are needed to indicate more widespread motor effects of MA abuse. However, it may also be argued that MA-induced neurotoxicity is different than that seen in Parkinson's disease or that other biological or environmental factors mitigate the expression of parkinsonism in MA-induced neurotoxicity that are not present in Parkinson's disease. Based on the preclinical literature reviewed above, we considered at least three factors that could explain the lack of an MA-induced parkinsonian phenotype in humans. These include the role of nicotine, tolerance to the neurotoxic effects of MA, and absence of comorbid hyperthermia.

Regarding nicotine, nearly all MA abusers smoke heavily. While prevalence data for comorbid nicotine among MA users is not known, published data from a study of injection drug users found that 91% were current cigarette smokers (Clarke *et al*, 2001). It has been shown repeatedly that nicotine reduces the risk of Parkinson's disease (Baron, 1986; Morens *et al*, 1995). Nicotine has been shown to prevent MA-induced nigrostriatal damage in rats (Maggio *et al*, 1998) via a mechanism thought to involve neurotropic factors and can reduce the locomotor sensitivity to MA in mice (Kuribara, 1999). Nicotine also inhibits monoamine oxidase (Berlin and Anthenelli, 2001; Castagnoli *et al*, 2002) enabling the greater bioavailability of striatal dopamine. Such nicotine-related mechanisms could compensate for MA-induced neurotoxic effects of dopamine neurotransmission and delay or minimize the development of parkinsonian motor signs.

The development of tolerance to the neurotoxic effects of MA may also explain the lack of an observable parkinsonian phenotype in humans. It has been shown that chronic MA exposure in escalating doses leads to behavioral and neurochemical sensitization (Gygi *et al*, 1996; Itzhak and Ali, 2002; Segal *et al*, 2003). Thomas and Kuhn (2005) observed that intermittent exposure to low doses of MA attenuated the microglial response and led to the development of tolerance to MA toxicity in mice. Animals pre-

exposed to MA showed less neurotoxicity (eg microglial activation) after MA exposure than acutely challenged mice. They concluded that this tolerance effect, at the level of the dopamine nerve ending, might serve as a neuroprotection response. If this effect can be observed across species, it might explain the lack of observable parkinsonism among intermittent MA users.

Hyperthermia is thought to mediate the neurotoxic effects of MA. Higher body temperatures facilitate neurotoxicity in MA-exposed animals possibly through an oxidative stress mechanism (Cadet *et al*, 2003). To our knowledge, there have been no studies clarifying the role of body temperature on clinical manifestation of MA abuse in humans. Studies of the behavioral effects of MA abuse in humans do not obtain contemporary information of body temperature. Insofar as hyperthermia is an important factor in the pathogenesis of MA-induced neurochemical changes (Xie *et al*, 2000; Broening *et al*, 2005), it would also seem that hyperthermia would be critical to the expression of behavioral abnormalities, such as parkinsonism. Considering other drug-induced conditions strengthens this argument. For example, hyperthermia and parkinsonism cooccur in neuroleptic malignant syndrome and serotonin syndrome (Gurrera, 2002; Mizuno *et al*, 2003). It is thought that parkinsonian rigidity and fever stem from a mechanism involving the balance of dopamine and serotonin in the basal ganglia and brainstem (Meigal and Lupandin, 2005). It is possible that MA-induced parkinsonism may depend on a disrupted thermoregulatory mechanism. Epidemiological studies are necessary to test whether environmental conditions are associated with the presence of a parkinsonian phenotype among MA users.

The primary question posed in this review concerns the ability of preclinical research on MA administration to inform the clinical condition. The preceding paragraphs highlight several important distinctions between preclinical and clinical findings that lead to two conclusions: (1) neurobiologic mechanisms underlying preclinical models of MA-induced hyperkinetic movement disorders correspond directly to the clinical presentation following acute exposure to MA; and (2) neurobiologic mechanisms underlying preclinical models of MA-induced parkinsonism do not necessarily translate to the clinical presentation, given the currently available research.

Conclusions

In animals, MA produces motor effects following acute and chronic exposure, suggesting separate mechanisms involving increase DA release and neurotoxicity, respectively. Effects of MA neurotoxicity include hyperthermia, locomotor abnormalities. Studies show that rodents develop tolerance to the neurotoxic effects, particularly during intermittent dosing regimens. In humans, acute MA exposure produces hyperkinetic motor effects similar to laboratory animals; however, the behavioral effects of longer-term neurotoxicity are not obvious. Significant differences in the expression of neurotoxicity and presence of multiple environmental and pharmacologic confounds may account for the lack of a parkinsonian phenotype in humans despite evidence of altered dopamine function. We argue that the results from animal studies of chronic MA

exposure do not necessarily translate to the clinical phenotype because of the protective effects of nicotine, an absence of hyperthermia, and tolerance stemming from intermittent use. Furthermore, the control of experimental variables in rodent research is very high, while human research will always be associational. It is also possible that the lack of an observable parkinsonian phenotype with chronic MA use is simply due to the use of insensitive measurements.

The key question stemming from this review is how is it that MA abuse leads to persistent damage to motor areas of the basal ganglia in humans, but that there are only few domains that show persistent behavioral deficits. Future studies can address this question. For example, because of its neuroprotective properties, it is important to control for the amount and extent of comorbid nicotine consumption when estimating prevalence of persistent MA-induced motor abnormalities. The question of whether hyperthermia is important in the pathophysiology of MA-induced dopamine neurotoxicity can be addressed by documenting body temperature at the time of the behavioral assessments. It remains unknown if comorbid fever emerged more often in a subgroup of MA abusers and whether these individuals are at greater risk for developing persistent parkinsonism. To address the question of whether individuals develop tolerance to the neurotoxic effects of MA, it is important to document patterns and time course of MA exposure. Parkinsonian motor disturbances may present to a greater extent among binge users compared to infrequent users. Lastly, studies can employ sensitive instrumental measures of motor function to detect subthreshold parkinsonian motor disturbances among chronic MA users. We have previously demonstrated that electromechanical devices and computerized analyses can detect mild subclinical parkinsonian motor signs that are overlooked using conventional observational methods (Caligiuri *et al*, 1993; Cortese *et al*, 2005).

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