Methamphetamine (MA) is a synthetic, powerfully addictive central nervous system stimulant drug, derived from amphetamine. It is used for both medicinal and illegal recreational proposes. MA causes an increase in activity, decrease in appetite, and a strong feeling of euphoria. It is used for both medicinal and illegal recreational proposes. MA causes an increase in activity, decrease in appetite, and a strong feeling of euphoria.

Pharmacology, neurobiology and neurotoxicity of methamphetamine

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Abstract

Methamphetamine (MA) is a synthetic, powerfully addictive central nervous system stimulant drug, derived from amphetamine. It is used for both medicinal and illegal recreational proposes. MA causes an increase in activity, decrease in appetite, and a strong feeling of euphoria. It is used for both medicinal and illegal recreational proposes. MA causes an increase in activity, decrease in appetite, and a strong feeling of euphoria. It is used for both medicinal and illegal recreational proposes. MA causes an increase in activity, decrease in appetite, and a strong feeling of euphoria.

Introduction

Methamphetamine (MA) is a synthetic, powerfully addictive central nervous system (CNS) stimulant drug, derived from amphetamine (AMP) having a similar chemical structure [1]. It is used for both medicinal and illegal recreational proposes. MA causes an increase in activity, decrease in appetite, and a strong feeling of euphoria, also referred to as “high” or “rush” [1-3].

MA is a schedule II stimulant, i.e. a drug with high potential of abuse available only through a prescription that cannot be refilled. It has been used, for the treatment of: (1) narcolepsy, (2) attention deficit disorder and (3) obesity (short-term use), but this use is limited [3]. Medicinal MA or “Desoxyn” is available in pure 5-10mg tablet form. Illegal MA or “speed” is available on the street and is normally presented as a white, odorous, bitter-tasting crystalline powder that easily dissolves in water or alcohol. It can be in pure or adulterated form, which may be diluted with non-psychoactive /psychoactive drugs. In 1995 the DEA reported street MA to be 54% pure at gram/and ounce level [2-5].

Epidemiological studies reports 34 million global MA users [6]. The US 2000 Substance Abuse and Mental Health Services Administration (SAMSHA) National Household Survey on Drug Abuse showed: (i) 4% of people had some lifetime MA use, (ii) 1.1% had used it in the past year and (iii) 0.5% had used in the past month [7]. In 2002, 5.3% had used MA in their lifetime, 0.7% in the last year [8]. The frequency of emergency room visits due to acute MA intoxication data has shown a dramatic increase in the past few years [7]. MA is highly abused by different age groups [5]. Greatest use is among men between the ages of 19 and 40 years, especially college students and young professionals involved in the club scene or attending rave parties [3-5, 8-11]. Use of MA by gay and bisexual males is very high [12]. MA dependence studies have shown that in certain populations, 50% to 75% of individuals with multiple AMP exposure develop dependence [13]. MA holds allure because it is cheap, easy to use and easily accessible. It has the potential to induce an abuse epidemic and become the most abused drug.

This review will present: (i) an overview of the neurochemical and pharmacological effects of MA administration, (ii) a summary of the clinical effects of MA administration and (iii) evidence of MA’s neurotoxic effects.

Neurochemical and Pharmacological effects

MA exerts powerful effects on several neurochemical systems throughout the brain. These include dopamine, GABA and GLU [14]. MA is highly lipophilic. This allows rapid and efficient transport across the blood-brain barrier and results in increased CNS penetration. It causes massive release of newly synthesized catecholamines, and blocks their reuptake from the synapse in several areas of the brain, including the nucleus accumbens, the prefrontal cortex and the striatum. This review presents: (i) an overview of the neurochemical and pharmacological effects of MA administration, (ii) a summary of the clinical effects of MA administration and (iii) evidence of MA’s neurotoxic effects.

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Pharmacological effects

MA targets DAT and blocks DA reuptake, (ii) reverse the direction of DA transport through the channel, (iii) displace DA from vesicular stores by occupying vesicular monoamine transporter (VMAT2), leading to increased DA release [4]. MA also potently inhibits monoamine oxidase (MAO) [1, 2, 20, 25-27]. Collectively these effects increase the catecholamine concentration in the synapse and the brain. Studies have shown that alpha-methyl-tyrosine (AMT) attenuates, whereas reserpine potentiates the releasing action of AMP [27, 28]. Acute and prolonged MA exposure can elevate postsynaptic...
nigrostriatal DA [14, 22]. Acute MA administration can result in increased dopamine turnover in the caudate nucleus, and changes in monoamines and peptides in the basal ganglia [14, 29, 30]. Acute administration of high and repeated doses of MA/AMP in monkeys, results in a transitory decline in DA in various brain regions. This might be due to temporary inhibition of tyrosine hydroxylase activity [28, 31-33] and in rats, repeated administration of low dose AMP results in a reduction in the number of DA receptors, but chronic administration of AMP in young guinea pigs results in behavioral supersensitivity [34, 35]. Inconsistencies in rodent data can be explained by the observation that chronic AMP treatment induces persistent changes in dopamine receptor sensitivity. This yields increased striatal DA receptor sensitivity and decreased response of dopamine receptors in the NAc [36].

Pharmacological effects of MA depend on the dose and pattern of administration. In animal studies, different effects are observed in rodents with (i) administration of a single dose, (ii) repeated administration of low doses at long intervals, (iii) repeated administration of high doses at short intervals and (iv) high-dose runs superimposed on chronic low-dose administration [37]. In humans, MA is usually ingested, smoked, snorted, or injected intravenously. The amount administered at every dose varies depending on factors such as; (i) route of administration, (ii) individual tolerance and (iii) purity. However, smoked or injected MA results in immediate and intense euphoria which lasts for several minutes and Ingested or snorted MA results in a less immediate, less intense, but longer lasting “high”. Intranasal and oral users experience euphoria after 3-5 minutes and 15-20 min of administration, respectively. This “high” may last 8-12 hours. AMP has a longer duration of action than cocaine (8-13 hours versus 1-3 hours) and thus has higher addiction potential [1-3]. Nearly 45% of MA is metabolized to amphetamine, and both are excreted by the kidneys [1].

Clinical Effects
In human clinical studies, MA naïve users show heightened alertness, attentiveness, and energy at low doses due to excessive stimulation of the sympathetic nervous system. Higher dose intoxication results in a sense of well-being, euphoria, and enhanced self-esteem that can approach hypomania and grandiosity [1]. Sexual activity and pleasure is increased with initial use, this decreases with time and use. Longer use is associated with impaired sexual functioning in males, a phenomenon known as “crystal dick” [12]. Adverse effects include restlessness, insomnia, bruxism and excessive weight loss due to appetite suppression [11, 38]. Fetal studies show that MA crosses the placenta and concentrates in fetal tissue. Further studies have shown decreases in: (i) visual recognition memory, (ii) IQ, (iii) mathematical and language skills, (iv) poor social adjustment, and (v) aggressive behavior in children with prenatal stimulant exposure [2].

Chronic use of MA results in catecholamine depletion, and leads to “crash” (almost lifeless state lasting 1-3 days). Marked psychiatric complaints such as psychotic and anxiety disorder-like states are associated with chronic MA abuse [39-42]. Obsession with minute details progressing to compulsive repetitious behaviors is also observed. Skin picking is very common and is accompanied by “delu-
given low dose MA eight times per day. This dose was increased as they became tolerant to the debilitating effects of the drug. They were receiving a total dose of 52 mg/kg per day for a period of four to six months. They were sacrificed after six months and regional brain assay of transmitter levels was conducted. It was observed that MA treated monkeys had significantly reduced regional DA and NE levels with respect to control monkeys. This experiment clearly showed that the repeated administration of MA caused permanent neuron changes [22, 46, 57]. Further studies exploring species differences to MA administration showed, a marked decrease in nigral and striatal TH activity of rats following repeated doses of methamphetamine [45]. MA metabolism studies showed that rhesus monkeys, guinea pigs and humans metabolize MA through oxidative deamination, while rats metabolize the compound primarily through parahydroxylation [58]. In another study, Wagner et al administered high doses of MA to groups of rats and guinea pigs for a period of 30 days. The total daily dose of 50 mg/kg was divided into two subcutaneous injections spaced twelve hours apart. The animals were sacrificed two weeks following the last injection and regional brain assays were performed. Results showed that: (i) striatal DA levels of drug-treated subjects were depleted to about 50% of control values and (ii) these depletions appeared to be dose dependent [59]. These findings collectively showed that repeated administration of MA caused long-lasting depletions of central DA lasting six months in rhesus monkeys and two weeks in rodents. Wagner et al in the same experiment administered high doses of MA to another sub group of rats for 30 days. The rats were sacrificed 2, 4, or 8 weeks after the last injection and regional brain assay was done. Results showed significant depletion of striatal DA after all three waiting periods. No recovery was observed over the 8-week waiting period, and depletion was the same even after 6 months of the last injection [60, 61].

In another study, groups of rats received different daily doses of MA (12.5, 25, or 50 mg/kg per day) for 40, 20, or 10 days, respectively, such that each rat received the same total dose of MA. After 2 weeks from the last injection they were sacrificed. The results showed significant striatal DA depletions in rats receiving two higher doses of MA. In a counterpart to this study, groups of rats received 12.5, 25, 50, or 100 mg/kg per day for four days; all other parameters were the same. Similarly, rats receiving two larger daily doses of MA showed DA depletions [60]. These findings suggest that low clinical dose of MA even for prolonged periods resulted in minimal brain dysfunction and might not be associated with neuronal damage in humans. Further exploration in primates showed higher sensitivity to AMP compared to rodents. In recent studies researchers administered 2.0 mg/kg of AMP or MA to vervet monkeys in two IM injections, 4-hours apart. They observed substantial and long-lasting depletion of striatal DA after one month, but reported a partial recovery by three months [31, 62]. The 2.0 mg/kg dose used in these studies was considerably lower than those used in earlier rodent studies, but the magnitude of the DA depletion was quite comparable. This finding indicates that primates have higher AMP neurotoxicity sensitivity than rats. DA recovery was observed in monkeys, but not in the rodents, nor in the monkeys treated with the higher doses of MA. This might be because the MA doses administered to the vervet monkeys were comparatively low doses administered in just a few injections via a different route as compared to earlier rhesus monkey and rodent studies.

More recent rat studies have shown degeneration of DA nerve fibers, loss of tyrosine hydroxylase, DA transporter, tryptophan hydroxylase, and loss of 5-HT-immunoreactive axons and axon terminals following a high dose of MA [10, 63, 64]. Many studies have shown that MA use results in damaged striatal DA nerve terminals and DA cell bodies in substantia nigra (SN), pars compacta, and ventral tegmental area (VTA) [64]. These finding provided neuroanatomical evidence of neurotoxic effects of MA. Studies profiling duration of neurotoxicity in animals have shown long term neurotoxicity following administration of high doses MA, which spans from months in rats to years in monkeys [32]. The extent of dopaminergic and serotonergic neurotoxicity caused by AMP analogs depends on several factors including: (a) specific amphetamine analogs, (b) animal species, (c) mouse strain, (d) dosage and frequency of drug administration and (e) the ambient temperature of drug administration and the thermoregulatory effect of the drug [22, 49, 65]. Rats administered with 10 to 15 mg/kg MA every 6 hours for 5 doses, showed decreased TH activity and DA content in the neostriatum within 18 hours after the first dose [66, 67]. Administration of 5 mg/kg of MA, every 3 hours to Swiss Webster mice caused selective depletion of striatal DA, DA metabolites 3,4-dihydroxyphenylacetic acid (DOPAC), homovanillic acid (HVA) and DAT binding sites, with no evidence of 5-HT depletion [23]. MA induced neurochemical deficits persist for extended periods of time even after the drug is discontinued in rats and monkeys (4 years) [68, 69]. Thus, from the above mentioned data we can conclude that MA/AMP exert toxic effects in a variety of animal species and the MA-induced changes appear to be long-lasting and in some cases, may be permanent. Further experiments across species are necessary to elucidate the functional consequences of MA induced neurotoxicity.

Human studies
In 1990s researchers started looking at the effects of AMP/MA in humans. Wilson et al in 1996 conducted post-mortem analyses of brain tissue from humans who had abused AMP long before they had died and controls. They reported that, AMP abusers had deficits in DA, TH activity, and the DAT in the NAc, caudate, and putamen indicating that AMP abuse damaged the striatal DA system [70]. These findings might explain the rationale for the dose escalation and dysphoria that are frequently found in MA abusers, and also help us better understand persistent psychosis and paranoia reported by MA abusers [41, 70]. Neuropsychological studies in MA abusers have shown an association between severity of AMP dependence and poorer performance on measures of memory, attention and concentration [71, 72].

Preliminary neuroimaging studies in MA abusers suggest that MA may be neurotoxic. Magnetic resonance imaging (MRI) has showed cerebral infarcts and hemorrhage in some individuals who develop neurological complications after MA use [73, 74]. Two qualitative SPECT (199mTc-HMPAO) studies demonstrated ‘multiple perfusion defects’ in both active users and in abstinent METH users [75, 76]. Recent PET studies have shown that there are long-lasting reductions in striatal DAT in previous MA or methcathinone abusers [48]. Lower DAT density in NAc, PFC, and the caudate/putamen of MA users is seen compared to controls. MA users also exhibited psychiatric symptoms, the severity of which was significantly correlated with the duration of MA use [77]. Volkow et al, showed significant

reduction in the DAT density of MA abusers in the caudate (28%) and putamen (21%), which was associated with motor slowing and memory impairment [78]. Chang et al, in 20 abstinent MA abusers, found deficits in working memory tasks compared to matched controls. Perfusion magnetic resonance imaging (pMRI) studies of these subjects showed an increase in regional cerebral blood flow (rCBF) in several parietal regions and a decrease in rCBF in putamen regions. These changes indicate possible neuronal damage [79]. Using FDG-PET, Volkow et al showed decreased glucose metabolism in the thalamus and striatum, but increased metabolism in the parietal cortex of abstinent MA users [80]. Ernst et al, using Proton MR spectroscopy (1H MRS), reported decreased concentrations of N-acetyl (NAA) compounds in the frontal white matter and the basal ganglia, and increased choline (Cho) and myo-inositol in the frontal cortex of abstinent MA abusers. These results suggest neuronal damage of frontal white matter and the basal ganglia; and gliosis of frontal cortex [19]. Other MRS studies have found: (i) evidence of abnormally low normalized NAA (i.e., NAA/Cr) levels and higher normalized Cho (i.e., Cho/Cr) levels in the anterior cingulum (ACC), with no evidence of such findings in the primary visual cortex in recently abstinent MA subjects, and (ii) evidence of low NAA in the anterior cingulum and a trend toward a low NAA value for the basal ganglia [1, 81]. These MRS findings are interpreted as consistent with neural damage to the frontostriatal regions. A functional MRI study of 10 METH users reported decreased prefrontal activation and elevated parietal activation during tasks that involved decision-making [82]. The imaging findings show that chronic MA abuse causes alterations in brain structure and function.

Moszcynska et al, in a recent post mortem study compared dopamine levels in autopsied brain tissue of chronic MA users with those in patients with Parkinson’s disease and in a control group. They reported reductions in mean dopamine levels in the MA users more in the caudate (~61%) than in the putamen (~50%) [83]. This finding of reduction in the caudate explains cognitive disturbances in chronic MA users. Chang et al, in a structural MRI study, recently reported both striatal and pallidal enlargement in abstinent MA abusers. MA abusers showed larger globus pallidus (9.6%) and putamen (9.9%) volumes compared to age and gender comparable controls. Chang has suggested structural enlargement might be due to inflammation and reactive gliosis induced by striatal injury caused by long term MA abuse [84].

Studies profiling duration of MA neurotoxicity in humans have been mixed, with conflicting findings. McCann et al in a PET study showed reduced striatal DAT density in chronic MA abusers after three years of abstinence. This suggests that chronic MA abuse leads to destruction of DA nerve terminals or cell bodies [48]. In a recent PET study, Volkow et al reported DAT normalization, but no change in cognitive deficits following DAT normalization in a paired study of five subjects that were initially examined in early abstinence and then in late abstinence (1.5 to 2 years). Volkow et al have suggested that DAT recovery might be due to increased arborisation or transporter protein up regulation on surviving DA terminals. This could lead to normalized ligand binding in imaging studies, but it may not be sufficient to fully restore the dopaminergic neurotransmission that subjects need in order to resume baseline neuropsychological functioning [85]. This finding suggests that chronic exposure to methamphetamine does not necessarily cause permanent deficits or damage to the DA system in human users. Autopsy studies in MA abusers have shown marked decreases in striatal TH, DAT, and DA, but preservation of the presynaptic DA markers VMAT and DOPA decarboxylase without any signs of pigmented cell loss in the substantia nigra [70, 83]. Collectively, these findings suggest that MA-induced neurotoxicity leads to selective destruction/down-regulation of particular DA synthetic and functional proteins rather than to general destruction of DA terminals or cell bodies [70]. Thus, findings from neuroanatomical, neurochemical, neuropsychological, imaging and postmortem data support the conclusion that methamphetamine abuse causes damage to multiple transmitter systems that are distributed throughout the brain. Whether the ensuing damage is permanent or reversible over time has not yet been determined, but additional studies are needed to address this important issue.

Mechanisms of Neurotoxicity

The mechanisms involved in MA induced neurotoxicity are still unclear. Studies have implicated reactive oxygen species and the resultant oxidative stress. Studies investigating the role of DA in inducing MA neurotoxic response, showed that pre-treatment with DA synthesis inhibitors, such as alpha-methyl-p-tyrosine (AMT) provide protection against MA induced neurotoxicity to both DA and 5HT systems. Similarly, treatment with L-DOPA restored the capability of MA to induce neurotoxicity. These findings provide evidence indicating that endogenous DA is required for MA induced neurotoxicity [44, 53, 86]. In addition, Seiden et al in a rat study showed that following a single injection of MA (100 mg/kg), 6-hydroxydopamine (0.39 +/- 0.31 nanograms/mg of tissue at 2 hr) was formed in the caudate nucleus. They also showed a 50% depletion of caudate dopamine at 2 weeks post MA administration. This suggest that MA treatment leads to the formation of 6-hydroxydopamine from endogenous dopamine which is responsible for the MA induced neurotoxicity to dopamine terminals [87]. Severity of MA-induced neurotoxicity studies showed that MA induced neurotoxic insult is influenced by the levels of: (i) reducing enzyme super-oxide dismutase (SOD), (ii) ROS-producing enzyme neuronal nitrous oxide synthase (nNOS), and (iii) antioxidant ascorbic acid [23, 65, 88]. Studies of VMAT-2 knockout mice showed, increased damage to DA system after MA treatment. This finding suggests that MA might redistribute DA from the synaptic vesicle (reducing environment) into the neuron’s cytoplasm (oxidizing environment). This redistribution would result is the generation of free radicals and reactive metabolites that likely lead to protein and cell membrane destruction [21].

Limitations of Methamphetamine Neurotoxicity Research

Animal studies
Animal research advocates have claimed “animal models” to be reliable models of human conditions as they are conducted in “controlled” laboratory environments. Considerable work has been done with regards to MA neurotoxicity in animals. These studies have reported consistent positive findings, showing that MA administration results in neurotoxicity. However, there are concerns with regards to the clinical relevance of these studies. These are: (i) interspecies differences in anatomy and physiology, (ii) differences in cause and course of MA neurotoxicity between human and animal, and (ii)
stress (due to caging, social disruption, restraint, transport, and repeated handling) experienced by animals in laboratories. These factors can invariably alter research results. Many MA neurotoxicity studies have shown disparity across different species with regards to (i) MA exposure, (ii) severity of MA induced insult, (iii) duration to which toxic effects are observed, and (iv) pattern of recovery from MA induced neurotoxic insult. Most rodent studies have used an acute regimen of a high dose of MA/AMP given within 8-72 hours. This is in complete contrast to the human model of MA abuse which extends over a period of weeks, months and years. Scientist involved in rodent studies have advocated the use of “acute model” claiming its relevance to the final outcome i.e. MA induced neurotoxicity. Skeptics of this model are of the opinion that patterns of abuse influence the degree of neurotoxic damage. Explanation given by animal researchers to this concern is that “acute dosing model” in rodents may resemble the “binge pattern” of drug abuse in humans. The issue of “sensitivity” differences to psychoactive drugs is another important concern in MA animal model research. It has been observed that “sensitivity” differences do exist in rodents and humans: the dosage of AMPs given to rodents exceeds the dosage abused by humans. These dose differences are explained by difference in diverse pharmacokinetics and pharmacodynamics of the drug in rodents and humans. Animal model studies are not good predictors of clinical symptoms/behavioral effects due to AMP/MA neurotoxicity, as animals cannot reveal subjective effects (headache or psychological effects) post MA administration. Thus, animal studies have limited functional significance in their ability to predict MA neurotoxicity in humans.

Human studies
Since the 1990s researchers have been looking at the effects of AMP/MA in humans. Many studies have been conducted looking at the neuroanatomical, neurochemical, neuropsychological, imaging and postmortem changes associated with MA abuse. They have shown that MA abuse causes damage to multiple transmitter systems, distributed throughout the brain. Although these studies showed positive findings, they have significant methodological limitations. Earlier studies have failed to capture vital data on: (i) the parallel use of other drugs, (ii) length of abstinence periods. Drug specificity is an important parameter in assessing neurotoxicity. Poly-drug abuse (alcohol, cannabis, cocaine) in human MA abusers makes it difficult to delineate the specific neurotoxic effects of MA. Thus data from studies, utilizing poly-drug abusers and reporting neurotoxic effects of AMP/MA is not very credible, as it does not show the specific effects of MA on human subjects. Data from studies examining the effects of low prescribed MA doses (for minimal brain dysfunction or reduction in food intake) can help in understanding specific deleterious effects on the dopaminergic system caused by MA. Length of abstinence periods is important in assessing duration of MA induced neurotoxicity and recovery. Failure to capture this data impairs our ability to interpret the long-term effects of MA. Recent studies also exhibit methodological weaknesses without an obvious solution to date, i.e. (i) inadequate MA dependent group, (ii) questionable reliability of statements/histories by the subjects themselves on their current and earlier drug abuse habits, (iii) difficulties recruiting adequate control groups, (iv) uncertainties related to the precise chemical composition of “cut” MA. Robust sample size is important in elucidating clinical neurotoxic effects of MA. Many studies reporting MA induced deficits lack sample size and/or both genders. These factors decrease the significance of their results and its application to the general MA user population. Inaccuracy in clinical history and history of drug use by the subjects is a serious limitation in interpreting human MA neurotoxicity results. Most of the studies are retrospective, relying on participants’ self-report. This makes it difficult to ascertain the amount and type of drug used by the participants, thus reducing the reliability of the findings. Retrospective studies also lack in their ability to determine differences between control and user groups prior to MA use. Control groups are important in assessing the extent of neurotoxicity caused by MA. Many studies have used poorly matched control groups that include non-users, and poly-drug users with overall moderate use patterns than the poly-drug MA users. Studies have shown illegal/street MA to be impure as it is diluted/cut with other psychoactive active substances (ketamine, dextromethorphan, AMP, MDMA, ephedrine and salicylates), which makes it very difficult to confirm whether the neurotoxic effects exhibited by MA abuser are MA specific or are the cumulative effects of other psychoactive substances. Recently, brain imaging studies have provided much needed insight in the structural and functional aspects of the brains of living MA abusers. These studies provide important information on how MA changes the structure and functioning of specific brain regions. However, limitations of this technique in humans make it difficult to determine conclusively that brain cells are damaged or destroyed as result of MA abuse. Another important limitation observed in some brain imaging studies was that neuropsychological and cognitive testing was performed in MA abusers and not in controls. Thus, it is not possible to determine the extent to which MA abusers differed from controls. Thus, human MA neurotoxicity research has a number of significant limitations which impair our understanding of the extent of MA induced neurotoxicity. At present, we are unable to completely rule out the influence of comorbid factors. More methodologically sound research is required to fully understand the extent and duration of neurotoxicity induced by MA.

Remaining challenges
Since 1976, significant progress has been made in elucidating the neurobiology of MA/AMP, but still a number of challenges are remaining. The exact mechanism of MA induced neurotoxicity is very elusive. Studies have shown the possible involvement of transporter and temperature in the expression of MA induced toxicity of the DA and SHT neurons [49]. However, studies in this area haven’t explored the resistance of NE neurons to this toxic effect. NE neurons exhibit similar properties as DA and SHT neurons, with the exception of resisting MA/AMP induced neurotoxicity. Studies exploring differences between DA and NE neurons may help in identifying features of DA neurons that predispose them to MA/AMP neurotoxicity. Studies have shown that DA and SHT cell bodies are spared from MA/AMP neurotoxicity, even in the worst case of MA administration. Research in the area of neuron vitality should explore factors vital to the health of the axons and axon terminals. This would help in identifying candidate processes involved in AMP-induced injury. If candidate genes important to axonal integrity are identified, focused and testable hypotheses regarding mechanisms underlying neurotoxicity could be generated using present advances in genomics and proteomics.
Different species respond differently to MA insults. Murine research has shown increased DA toxicity (possible vulnerability) and no or little 5-HT toxicity (possible resistance) following MA/AMP administration. Further analysis of a possible selective response mechanism could help in: (i) predicting the effects of AMP in other animal species, and (ii) may also help in understanding the mechanisms of AMP toxicity. Primates exhibit long-lasting toxicity, whereas rodents tend to recover from AMP analogue neurotoxicity over time. Similarly, Volkow et al (2001) have shown DAT recovery in human MA abusers with protracted abstinence [85]. Exploration of factors involved in the duration of toxic injury across different species, could help in devising methods for reversing injury. Studies exploring possible neuronal recovery factors would have great implications for a variety of neurodegenerative conditions. These studies should also define possible recovery characteristics if it occurs (reinstatement of original, normal neuronal pathways/aberrant re-innervation) and its consequences.

Functional consequences are integral to MA neurotoxicity research. Animal studies have discussed abnormal dopamine-mediated behaviors following MA/AMP-induced DA and 5-HT neurotoxicity [89]. Functional research in this area could provide potential clues to: (i) similar damage in humans, and (ii) further findings in the role of DA and 5-HT in normal behaviors.

Many researchers have shown evidence of MA-induced DA neurotoxicity in humans [48, 77, 85]. There are still grey areas in this field with regards to the (i) doses and drug regimens needed to produce neurotoxicity in humans, (ii) the functional consequences of neurotoxicity, and (iii) potential long-term clinical implications of MA toxicity (vulnerable to Parkinson’s disease with advanced age). Furthermore, epidemiological studies focusing on the prevalence of a variety of neurologic and psychiatric conditions (e.g. movement disorders, depression, anxiety disorders, sleep disorders) in individuals exposed to these drugs relative to the general population are in order.

Conclusions & Future directions
MA exerts powerful effects on several neurochemical systems throughout the brain including dopamine, GABA and GLU. It causes a strong feeling of euphoria, which creates a potential for addiction and abuse. Epidemiological data suggests a progressive increase in the MA epidemic all over the world, with its use highest in younger male cohorts. MA has a longer half-life: this may produce exceptionally long-lasting toxic effects. Abrupt cessation results in depression, dysphoria, suicidal ideation, irritability, and agitation. Neuro-cognitive impairments that affect information processing, verbal memory and other domains of cognition are commonly seen in MA abusers.

MA neurotoxicity research has shown a number of factors influencing the nature and degree of toxicity. These include (i) dose, (ii) dosing interval, (iii) route of administration, and (iv) temperature. Up-to-date neurotoxicity research shows that MA abuse causes: (i) serious cognitive impairments in humans, and (ii) DA and 5HT neurons damage in rodents. Focused research elucidating functional consequences of MA induced toxicity in animals and humans is needed. Concentrated efforts should focus on (i) mechanisms by which MA leads to selective DA and/or 5-HT damage, (ii) mechanisms, time course and features of recovery and (iii) MA’s involvement in neurodegenerative diseases (Parkinson’s disease).

It is very important to develop research strategies towards prospective designs, looking at large cohorts of young people (not MA users) belonging to a risk group for recreational drug use (attendants of rave parties/ bisexual and gays). Following-up on them over years and re-examining them, recording drug histories using psychometric instruments and carrying out neuropsychological tests. These efforts, could help in better understanding of (i) relation between drug use and “sub-clinical” psychological symptoms or “neuro-cognitive” failures and, (ii) questions regarding progression, persistency and reversibility (if any) of the MA induced alterations. There will always be debate about ethical aspects of such studies, but they are definitely needed to determine the answers to the important questions around possible long-lasting adverse effects of MA on the human brain.

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