Review

Memory impairment induced by amphetamine derivatives in laboratory animals and in humans: a review

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Abstract

The 20th century brought with it the so-called club drugs (the most notorious being amphetamine derivatives), which are used by young adults at all-night dance parties. Methamphetamine and 3,4-methylenedioxymethamphetamine (MDMA or ecstasy) are synthetic drugs with stimulant and psychoactive properties that belong to the amphetamine family. Here, we have reviewed the literature about the cognitive impairment induced by these two amphetamine derivatives and the pre-clinical and clinical outcomes. Although there is controversial evidence about the effect of methamphetamine and MDMA on learning and memory in laboratory animals, results from published papers demonstrate that amphetamines cause long-term impairment of cognitive functions. A large number of pharmacological receptors have been studied and screened as targets of amphetamine-induced cognitive dysfunction, and extensive research efforts have been invested to provide evidence about the molecular mechanisms behind these cognitive deficits. In humans, there is a considerable body of evidence indicating that methamphetamine and MDMA seriously disrupt memory and learning processes. Although an association between the impairments of memory performance and a history of recreational amphetamine ingestion has also been corroborated, a number of methodological difficulties continue to hamper research in this field, the most important being the concomitant use of other illicit drugs.

Keywords: ecstasy; humans; laboratory animals; learning; MDMA; memory; methamphetamine.

Introduction

Addiction is a complex aetiology involving the interaction of inherited predispositions and environmental factors that affects the brain and behaviour. Although many of the biological, environmental, and genetic factors involved have been identified, we still do not fully understand why individuals become addicted to drugs, or how these substances affect the brain in a such way as to foster compulsive drug abuse. In this regard, addiction also can be defined as a chronic, relapsing brain disease characterized by compulsive drug seeking and use, despite harmful consequences.

The 20th century witnessed the emergence of the so-called club drugs (the most important being amphetamine derivatives). These are commonly used by young adults at all-night dance parties, such as 'raves' and 'trances', in dance clubs and bars.

Methamphetamine, commonly known as 'speed', 'meth', and 'chalk', is a highly addictive stimulant that is closely related to amphetamine. Methamphetamine comes in two forms. One is a white, odourless, bitter-tasting powder, which is taken orally, snorted, or injected, while the other is a rock 'crystal', which is heated and smoked. In its smoked form, it is often referred to with street names, such as 'ice', 'crystal', 'crank', and 'glass'. It is long-lasting and toxic to dopamine neuron terminals in the central nervous system. According to the 2009 National Survey on Drug Use and Health, 1.2 million Americans had abused methamphetamine at least once in the year before being surveyed.

Methamphetamine differs from amphetamine in that at comparable doses, much more methamphetamine enters the brain, thereby making it a more potent stimulant drug (1). Like similar stimulants, methamphetamine is most often used in a 'binge and crash' pattern. The pleasant effects of this drug disappear even before its concentration in blood falls significantly, and users then try to maintain the 'high' by taking more. At present, there are no specific medications that counteract the effects of methamphetamine or that prolong abstinence and reduce the abuse by an individual addicted to this drug. However, a number of medications, such as bupropion, that are approved by the U.S. Federal Bureau of Investigation for other illnesses might also be useful for treating methamphetamine addiction (2).

The other amphetamine derivative with considerable prevalence as a 'club drug' is 3,4-methylenedioxymethamphetamine (MDMA or ecstasy). Belonging to the amphetamine family, this synthetic drug has stimulant and psychoactive properties. It is taken orally as a capsule or tablet and it is also hallucinogenic. While MDMA does not cause true hallucinations, many people have reported distorted time and perception while under its influence (3). Most people take MDMA orally, and its effects last approximately 4–6 h. Many users

will 'bump' the drug, taking a second dose when the effects of the initial one begin to fade. The typical dose of MDMA is between one and two tablets ingested in each session of night dancing, with each tablet containing from 60 to 120 mg. However, tablets of what users call ecstasy often contain not only MDMA but also a number of other drugs, including methamphetamine, caffeine, and cocaine (4).

Compared with methamphetamine, MDMA triggers a larger increase in serotonin and a smaller increase in dopamine release (5). Serotonin is a major neurotransmitter involved in regulating mood, sleep, pain, emotion, and appetite, as well as other behaviours. By releasing large amounts of serotonin, and also interfering with its synthesis, MDMA leads to a significant depletion of this key neurotransmitter. Consequently, it takes the human brain a significant amount of time to rebuild the store of serotonin required to perform crucial physiological and psychological functions.

Molecular, neuroanatomical, and neurophysiological studies have demonstrated mechanistic similarities between normal forms of learning and memory and the central actions of some reinforcing drugs. Drugs of abuse and Pavlovian and instrumental learning processes act on similar neural pathways in the mesocorticolimbic brain reward system (6–8). It has been suggested that some of the addictive potential of psychostimulant drugs of abuse, such as amphetamines may result from their capacity to enhance memory for drug-related experiences through actions on memory consolidation (9).

Preclinical studies of amphetamine derivatives-induced cognitive impairment

While there are a multitude of experimental models to assess learning and memory processes, most of the published studies with laboratory animals (mainly rats and mice) are devoted to two well-established paradigms: the novel object recognition test and the Morris water maze.

The object recognition task is based on the spontaneous tendency of rodents to explore a novel object. It has been proposed that this task is closely analogous to the recognition tests widely used in humans to test memory and to characterise amnesic syndromes by providing an accurate index of the overall severity of declarative memory impairment (10, 11). The development of object recognition memory and spatial water maze memory has been shown to depend on the hippocampus, and memory in both tasks is severely disrupted in animals with lesions in this brain area (12, 13).

Although spatial learning and memory in the Morris water maze is linked to hippocampal function (14–20), some studies have demonstrated that rats with dorsal hippocampus lesions did not show significant changes in the Y-maze test for short-term spatial memory, in the Morris water maze for long-term spatial memory, or in the T-maze delayed alternation test for working memory (21). Furthermore, disruption of hippocampal function by lesions, gene targeting, or pharmacological inhibition of glutamatergic N-methyl-D-aspartic acid (NMDA) receptors impairs Morris water maze spatial learning and memory while sparing cued learning (12, 22–25). It has been suggested that

Morris water maze-related stress may contribute to some of these impairments (26). NMDA antagonist-induced spatial learning impairments in the Morris water maze are reduced or eliminated by previous water maze experience (27, 28) as are those after saturation of long-term potentiation (LTP) (29). It is unclear whether these effects are the product of stress reduction or of transfer of training, in which animals learn general task characteristics in the non-spatial Morris water maze that facilitates later learning of the spatial version. LTP is the most studied form of synaptic plasticity in the hippocampus, and it is considered to be one of the cellular substrates of learning and memory (30). The involvement of LTP-like mechanisms in spatial learning has been demonstrated (31), specifically in the Morris water maze test (32).

Very recently, Dhonnchadha and Kantak (33) have reviewed the relationship between brain sites whose learning, memory, and executive functions are impaired by chronic drug use (e.g., alcohol and amphetamine). Unfortunately, in general, most of the available tasks considered to measure cognitive processes that are disrupted in several pathologies, such as schizophrenia (among them, working and/or recognition memory, delayed alternation task, or novel object recognition), have no capacity to distinguish between cognitive enhancers and antipsychotics (34).

There is controversial evidence about the effect of methamphetamine on learning and memory. A number of different authors (35–39) describe no impairments of learning or memory. On the contrary Vorhees' group and, more recently ourselves, reported that methamphetamine treatment impairs spatial learning and memory (40–43), whereas sequential learning in a multiple-T water maze is spared.

Belcher et al. (44) demonstrated that animals subjected to a binge methamphetamine dosing regimen that damages brain dopamine and serotonin terminals show impairments in a novel object recognition task. These impairments correlate with monoaminergic transporter loss in ventral caudate-putamen and hippocampus. Methamphetamine-treated rats show impaired object recognition lasting for at least 3 weeks after drug exposure (45).

Moreover, rats treated with methamphetamine show impaired recognition memory during the short-term memory test (object recognition task), whereas p-chloroamphetamine- and D-amphetamine-treated rats show scores comparable to controls. Results from Belcher et al.'s (46) study indicated that no single feature of methamphetamine-induced neurotoxicity is sufficient to produce the memory impairments seen after methamphetamine treatment.

From another point of view, prolonged methamphetamine abuse can lead to psychiatric symptoms and has been associated with various cognitive dysfunctions. The impact of self-administered methamphetamine on cognitive dysfunction and relapse was studied by Rogers et al. (47). Prolonged methamphetamine self-administration resulted in an escalation of daily intake and access-dependent impairments on novel object recognition; however, recognition of spatial reconfiguration was not affected, suggesting that prolonged contingent methamphetamine increases motivation for drug seeking after withdrawal while increasing cognitive deficits.

The results of Ito and Canseliet (48) demonstrate an aberrant regulation of hippocampal and basolateral-amygdala-dependent learning as a result of amphetamine exposure in mice. A behaviourally sensitizing regimen of amphetamine exposure has diverse effects on learning, memory, and cognition that are likely to be a consequence of long-term neural adaptations occurring in the cortico-limbic-striatal circuitry. In particular, altered dopamine signalling in the nucleus accumbens and medial prefrontal cortex has been implicated in amphetamine-induced changes in behaviour. Amphetamine alters the normal acquisition patterns of place and cue conditioning, significantly facilitating hippocampal-dependent place conditioning while attenuating basolateral amygdala-dependent cue conditioning.

Following withdrawal from D-amphetamine exposure, psychotic-like traits have been demonstrated, but the presence of cognitive deficits remains uncertain. Peleg-Raibstein and co-workers (49) performed a study with adult male Lewis and Fischer rats, differing in cognitive performance and exposed intermittently to escalating doses of amphetamine over 5 weeks. This treatment was effective in producing behavioural sensitisation to a subsequent amphetamine challenge. Following drug withdrawal, the animals were assessed in Pavlovian conditioning, object recognition, and spatial working memory. Amphetamine pretreatment induced similar behavioural sensitisation in both rat strains, but working memory was enhanced only in Fischer rats after withdrawal. Spontaneous novel object preference was enhanced in sensitized Fischer rats, but impaired in sensitized Lewis rats, thus effectively reversing the strain difference in non-sensitized controls. In this study, the authors concluded that the face validity of the amphetamine withdrawal model for cognitive deficits was limited to the object recognition memory impairment observed in sensitized Lewis rats. However, the possibility that enhancing dopaminergic neurotransmission may facilitate object recognition and spatial working memory performance was demonstrated in sensitized Fischer rats.

Nevertheless, the use of D-amphetamine as a memory enhancer is limited by a potent stimulatory side-effect profile caused by the release of dopamine. The laevo enantiomer of amphetamine is considerably less effective as a dopamine releaser and less potent in producing the stimulatory effects characteristic of D-amphetamine. Wiig et al. (50) demonstrated that L-amphetamine and L-methamphetamine do not increase locomotion or stereotypes beyond control levels, but they do produce significant memory enhancement. These compounds produced an effect comparable to that of D-amphetamine, but required only one quarter of the D-amphetamine dose to produce the same effect. The authors also found that, in hippocampal Arc/Arg3.1 protein synthesis, L-amphetamine modulates learning-induced changes that correlate with memory consolidation. These results suggest that L-amphetamine and L-methamphetamine are potent memory enhancers in rats and thus may ultimately be useful for treating memory disorders.

A novel rodent procedure (51) was designed to translate the *n*-back working memory task used in schizophrenic patients. Rats were trained in five-lever operant chambers to recall either the last (one-back) or penultimate (two-back) lever from random sequences of lever presentations of variable lengths. Although the possibility for mediating behaviours may exist, the rodent *n*-back task provides a clinically relevant model of working memory. Amphetamine and MK-801 (a selective antagonist of NMDA glutamate receptor subtype) produced selective impairments without disrupting response.

Preclinical studies about the effects of amphetamine derivatives-induced cognitive deficits are not restricted to rodents. A major hallmark of amphetamine sensitisation in both non-human primates and rodents is the manifestation of deficits in executive function and working memory. These deficits rely on the integrity of the prefrontal cortex, and thus may give significant insights into the cognitive dysfunction associated with addiction. Castner and Williams (52) demonstrated that repeated exposure to psychomotor stimulants in non-human primates leads to a corruption of neuroadaptive systems in the brain by an extraordinary influence on synaptic plasticity, learning, and memory. Actively harnessing this same process by repeated, intermittent D_1 agonist administration may be the key to improved working memory and decision.

Amphetamine exposure during development and behavioural consequences

Vorhees and co-workers (53) studied the spatial learning effects caused by developmental methamphetamine treatment in rats (postnatal days 11–20), and the selective effects on spatial navigation and memory. These authors demonstrated that spatial learning and memory impairments occur in three different strains of rats, in both males and females, in Morris mazes of different dimensions, and using differing procedures. These impairments occurred with and without previous experience in other tasks, with previous experience in related and unrelated tasks, and in the absence of impairments in swimming capacity. Altogether, these results suggest that the developmental effects of methamphetamine treatment on spatial learning may be a cause of concern for humans exposed to this drug during early brain development.

Adverse experiences early in life have profound influences on brain development, for example, by determining alterations in response to psychostimulant drugs. In this regard, D-amphetamine produces persistent recognition memory impairments, which are more pronounced when the animals are maternally deprived. This observation suggests that an early adverse life event increases the vulnerability of cognitive function to exposure to a psychostimulant later in life (54).

Smith and Chen (55) performed a study using Sprague-Dawley rat pups. These authors administered a milk formula containing 0, 5, 15, or 25 mg/kg/day of amphetamine intragastrically from postnatal days 4 to 9. After weaning, the effects of neonatal amphetamine exposure on hippocampus-mediated behaviour were assessed using the open-field, water maze, and conditioned taste aversion behavioural tasks. The results from these tests revealed that while amphetamine exposure during the spurt of brain growth alters behaviour in

open-field testing, it does not interfere with performance in the water maze or the conditioned taste aversion paradigm. These results led the authors to conclude that the effects of neonatal amphetamine exposure on hippocampus-mediated behaviours are related to interactions between the temporal (time of drug exposure) and regional (different regions of the hippocampus) vulnerability issues.

Acevedo et al. (56) performed an interesting study about the involvement of histamine in mediating the long-term effects of methamphetamine administered to mouse neonates. Exposure to this substance early in life causes sex-dependent impairments in object recognition, spatial learning, and memory in the water maze, and prepulse inhibition in adulthood. These impairments are mediated by histamine since increasing the release of this neurotransmitter mimicked (and also the contrary is true) the impaired long-term effects caused by methamphetamine. More recently, Siegel et al. (57) demonstrated that the cholinergic system also plays a key role in the long-term methamphetamine-induced cognitive deficits in mice exposed to methamphetamine from postnatal days 11 to 20 and behaviourally tested in adulthood.

In the case of MDMA, prenatal (from E14 to E20 in the rat) administration of this amphetamine derivative does not affect performance in the radial arm maze or the Morris water maze, but treated animals demonstrated altered performance in a cued Morris water maze paradigm (58). These findings suggest that prenatal exposure to MDMA results in a behavioural phenotype in adult rats characterized by reduced anxiety, a heightened response to novelty, and 'hyperattentiveness' to environmental cues during spatial learning.

Skelton and co-workers (59) demonstrated that MDMA exposure has adverse effects on the developing brain and behaviour. Evidence to date has shown that developmental exposure to this substance results in learning and memory impairments in the Morris water maze in adults. Moreover, neonatal MDMA exposure increases the sensitivity of the serotonin 5-HT$_{1A}$ receptor subtype, a possible mechanism underlying the learning and memory deficits seen. Very recently, Rodsiri and co-workers (60) provided evidence of long-term disruption of novel object discrimination following 'binge-type' repeated MDMA administration. However, this impairment of recognition and working memory is not directly related to any neurotoxic loss of serotonin neurons since brain serotonin content was unaltered. Further studies are required to establish the mechanism underlying this change.

Chronic amphetamine treatment during peri-adolescence results in altered behaviour in the Y-maze and persistent down-regulation of hippocampal cyclic AMP response element binding protein (CREB) mRNA expression. Given that this group had intact spatial learning and reference memory, it would appear that the deficits observed in the Y-maze reflect a dysfunction in response to novelty. No effects of amphetamine treatment were observed in the adult cohort; thus, these data suggest idiosyncratic sensitivity of peri-adolescence to the long-term effects of psychostimulants (61).

Receptor pharmacology and amphetamine-induced cognitive deficits

Methamphetamine and MDMA interact with a variety of pharmacological receptors, the most important being dopamine and serotonin receptors. This interaction is involved in the cognitive impairment induced by these amphetamine derivatives. A large number of pharmacological receptors have been studied and screened as targets of amphetamine-induced cognitive dysfunction.

Initially, studies addressing the involvement of neurotransmitter receptors and amphetamine-induced cognitive deficits were centred on serotonin and dopamine receptors. High expression of 5-HT$_6$ receptors in the hippocampus, nucleus accumbens, and striatum had been considered consistent with a potential role in cognition. Furthermore, Ro4368554 (a selective antagonist of this serotonin receptor subtype) enhanced learning and memory processes in unimpaired and scopolamine-impaired rats, supporting the idea that the cognitive enhancing effects of 5-HT$_6$ receptor antagonists involve modulation of cholinergic neurotransmission (62). A number of 5-HT$_6$ antagonists are currently in clinical development for Alzheimer's disease; however, there is some discrepancy regarding cognitive efficacy in subjects, and only limited data are available on the function of the 5-HT$_6$ receptor in animal models (63).

Selemon and co-workers (64) examined the involvement of dopamine D$_1$ receptor subtype in the cognitive dysfunction induced by amphetamines in laboratory animals. They performed an elegant study about the capacity of a chronic treatment (for up to 8 months) with the selective dopamine D$_1$ receptor antagonist SCH39166 to reverse cognitive impairment associated with amphetamine sensitisation in nonhuman primates. Cognitive testing was performed before, during, and for up to 18 months following treatment. The results obtained suggest that the deleterious consequences of amphetamine sensitisation can be reversed by modulation of D$_1$ receptor signalling.

Like Selemon's study, several lines of evidences indicate that the dopamine D$_4$ receptor subtype is also a selective dopamine target that could mediate cognitive and striatal motor processes. Woolley and co-workers (65) studied the effects of a selective dopamine D$_4$ receptor agonist, A-412997, and demonstrated that this compound improved a temporally induced deficit in the rat novel object recognition task at doses 10-fold lower than those stimulating activity. In contrast to amphetamine, A-412997 did not mediate reward-related behaviour in the conditioned place preference paradigm. These data indicate that selective activation of the D$_4$ receptor may represent a target for the treatment of cognitive impairment without the potential drug abuse liability associated with psychostimulant therapies.

The potential role of acetylcholine receptors in mediating the effect of amphetamines has also been examined. Nair and Gudelsky (66) determined the influence of a serotonin-depleting regimen of MDMA on subsequent stimulation of acetylcholine release in the prefrontal cortex. These authors demonstrated that although MDMA-induced serotonin

depletion diminishes subsequent MDMA-induced acetylcholine release, there is little impact on cortical acetylcholine release elicited by the stress of pain or the novelty of an environmental intruder. In another study, AC-260584, a potent and selective muscarinic M_1 receptor agonist, enhanced performance in the Morris water maze during a probe test after 6 days of training, similar to the positive control tacrine. Moreover, this compound reduced amphetamine-induced hyperactivity and apomorphine-induced climbing, consequently reducing liability for extrapyramidal symptoms (67).

The involvement of nicotinic receptors in the neurotoxic effects of amphetamine derivatives has been extensively addressed by our research group (68, 69). To evaluate the contribution of these receptors to the cognitive impairment induced by amphetamine derivatives, we performed several experiments to study the effect of memantine in preventing both the methamphetamine- and MDMA-induced cognitive impairment in Long Evans rats. Memantine is a low- to moderate-affinity NMDA receptor antagonist that improves performance in several pharmacological models of impaired learning and memory (70) in rats, as well as in patients with moderate to severe Alzheimer's disease (71). Additionally, memantine is an antagonist of specific α7 nicotinic receptors (72). Amphetamines were administered to animals at doses of 10 and 15 mg/kg. Using the interspecies scaling formula [dose human = dose animal (WT human/WT animal)$^{0.7}$ (WT, weight)], these doses are equivalent to a dose of 188 mg in a 70-kg human, which may be lower than the doses used by chronic abusers (73) and creates similar plasma concentrations of amphetamines to those of a human consumer (74). Our results demonstrate a specific effect of methamphetamine or MDMA treatment on the object recognition memory test in rats. The capacity to discriminate between the familiar and the novel object was abolished following both protocols and animals pretreated with memantine recovered the lack of discrimination that appeared in the methamphetamine- and MDMA-treated animals. This beneficial effect of memantine was assessed by the partial recovery of the discrimination index value and appeared to be a consequence of antagonism of memantine at glutamic acid and α7 receptors (40, 75).

Molecular biology of learning and memory dysfunction induced by drugs of abuse

Since the middle of last century, a number of research efforts have been focused on demonstrating the molecular mechanisms of cognitive deficits induced by amphetamines. Recently, emerging evidence indicates that epigenetic alterations to the genome, including DNA methylation and histone modifications, are crucial mechanisms underlying addiction and the neurobiological response to addictive substances, such as amphetamines (76).

In a very recent paper, Upadhya et al. (77) addressed the involvement of cocaine- and amphetamine-regulated transcript peptide (CART) in spatial learning and memory. In this study, CART-administered rats showed a significant reduction in escape latency and spent more time in the platform quadrant in the Morris water maze during the retrieval protocol. CART immunoreactivity in the arcuate and paraventricular nuclei, central nucleus of amygdala, bed nucleus of stria terminalis, nucleus accumbens, dentate gyrus, and thalamic paraventricular nucleus was significantly increased after 4 days of training. Moreover, CART-antibody and scopolamine produced the opposite effect. This finding thus demonstrates that CART promotes spatial learning and memory and navigational experiences in Morris water maze and also up-regulates the endogenous CART systems in several areas of the brain.

Moreover, some neurotrophins, such as nerve growth factor and brain-derived neurotrophic factor (BDNF), have been described to exert relevant action on dopaminergic neurons involved in mediating the effects of psychostimulants (78). Recent studies have shown that activation of dopamine induces an increase in BDNF mRNA and protein expression in neuronal cultures and in selected brain regions, such as the striatum and hippocampus (79–81). On the contrary, deLima and co-workers (54) demonstrated that hippocampal BDNF content is not affected by D-amphetamine treatment. Furthermore, early life stress decreases hippocampal BDNF content and exacerbates recognition memory deficits induced by repeated D-amphetamine exposure. These observations would indicate that further experiments using intracerebral administration of BDNF and strategies to inhibit BDNF signalling (i.e., using RNA interference) are required to clarify the role of this neurotrophin in mediating the effects of D-amphetamine.

In this regard, the function of the calcium-calmodulin-dependent protein phosphatase calcineurin (present in the hippocampus) in learning and memory has received a significant amount of attention as a result of its promotion of the dephosphorylation of CREB. Calcineurin is a key component in the transition from short-term to long-term memory (82), and its inhibition enhances learning and memory (83). Using antisense DNA against calcineurin, Ikegami and Inokuchi (84) demonstrated that an enhancement in LTP induction produced by the inhibition of calcineurin leads to an increase in memory strength in specific forms of hippocampus-dependent learning. The study carried out by Christie-Fougere and co-workers (85) showed that calcineurin inhibition extends the duration of conditioned olfactory memory and may provide a target for memory prolongation that is superior even to phosphodiesterase inhibition. Finally, in transgenic mice that express an active form of calcineurin specifically in forebrain structures and have a deficit in the transition from short- to long-term memory. Biala and co-workers (86) demonstrated that the calcium-calmodulin complex is involved in the long-term effects of drugs of abuse, such as amphetamine or opiates, inducing hippocampal-dependent learning and memory deficits.

Papaleo and co-workers (87) generated transgenic mice overexpressing a human catechol-*O*-methyltransferase (COMT)-Val polymorphism (Val-tg), and compared them with mice containing a null COMT mutation. Increased COMT enzyme activity in Val-tg mice resulted in impaired working and recognition memory, but blunted stress responses and pain sensitivity. Conversely, COMT disruption improved working memory but increased stress responses and pain

sensitivity. Amphetamine ameliorated recognition memory deficits in COMT-Val-tg mice but disrupted it in wild types, illustrating COMT modulation of the inverted-U relationship between cognition and dopamine. These results indicate that the *COMT* gene plays a critical role in an apparent evolutionary trade-off between cognitive and affective functions.

Finally, Plaza-Zabala et al. (88) studied the putative role of peroxisome proliferator-activated receptors in the cognitive impairment induced by amphetamines. The endogenous peroxisome proliferator-activated receptor α agonist, oleoylethanolamide, protects against these MDMA-induced deficits. Dopamine transporter binding sites significantly decreased 4 days after the last MDMA administration and pretreatment with oleoylethanolamide prevented this effect. These results suggest that oleoylethanolamide administration modulates the cognitive deficits induced by MDMA in a dopamine transporter-independent manner.

Memory impairment induced by methamphetamine and MDMA in humans

The ingestion of amphetamine derivatives by humans often involves repeated low-dose drug administration over a single short period, which is referred to as 'binge use' (89). It is important to denote that dose is a critical determinant of the cognitive effects of psychostimulants (90).

Social-cognitive difficulties are associated with methamphetamine use and have potentially important implications for rehabilitative practice (91). Methamphetamine is widely abused among young people. However, in this specific segment of population, the effects of methamphetamine use on neurocognitive performance are unclear. King and co-workers (92) demonstrated an impairment of executive functions in adolescent methamphetamine users, and Hoffman and co-workers (93) compared the general psychiatric and cognitive functioning of individuals dependent on methamphetamine and non-user controls. Methamphetamine-dependent individuals are more impulsive than controls, and this may be causally related to memory deficits but was unrelated to any other measure of psychiatric or cognitive impairment or any drug use history.

The notion that some methamphetamine users develop neuropsychological impairments while others with similar drug exposure do not implies that there are individual differences in vulnerability to the neurotoxic effects of this recreational drug. One source of differential vulnerability could derive from genotypic variability in the metabolic clearance of methamphetamine, which is dependent on the activity of CYP-2D6. Chana et al. (94) compared neuropsychological performance in 52 individuals with a history of methamphetamine dependence on the basis of their CYP2D6 phenotype. These authors proposed that efficient methamphetamine metabolism is associated with worse neurocognitive outcomes in humans, and implicated the products of oxidative metabolism of this substance as a possible cause of brain injury.

Furthermore, variation in the COMT val(158)met polymorphism has also been associated with executive cognition and working memory, presumably mediated by the prefrontal cortex. Hamidovic and co-workers (95) performed a double-blind, crossover design study with placebo or D-amphetamine. The results of this study suggest that the presence of the val allele is associated with poorer performance with a stimulant drug. These results further suggest that this polymorphism does not affect the mood-altering effects of D-amphetamine.

Methamphetamine use is associated with impairment in memory for intentions, or prospective memory, an episodic memory that involves the execution of a previously encoded intention at an appropriate moment in the future and is known to rely on the integrity of frontal systems. The findings of Iudicello's study suggest that individuals with methamphetamine dependence experience difficulty in the strategic components involved in the retrieval of future intentions (96).

Kalechstein and co-workers (97) examined the association between brain electrical activity, measured using quantitative electroencephalography and performance on measures of episodic memory in a sample of methamphetamine-dependent individuals who were evaluated after 4 days of monitored abstinence and non-drug-using comparison subjects. In methamphetamine users, but not in comparison subjects, increased θ power was correlated with poorer performance on the delayed recall subtests. There was no association between α, β, and δ power and performance in the memory tests. These results demonstrate that the electrophysiological abnormalities associated with methamphetamine dependence are likely to induce memory deficits when users are not intoxicated.

Recent evidence (98) has identified modafinil-related improvements in treatment outcomes for methamphetamine-dependent patients; however, the benefit to cognitive function, which is critical for treatment success, has yet to be examined. Nevertheless, there is an initial indication that modafinil reverses methamphetamine-associated impairments in working memory (99).

Rapeli and co-workers (100) demonstrated that individuals with former amphetamine dependence who had been abstinent for at least 1 year have normal cognitive function with the possible exception of verbal memory.

Recently, Cherner and co-workers (101) compared the neurocognitive functioning of methamphetamine-dependent participants who had been abstinent for an average of 129 days with that of demographically comparable control subjects with similar level of education and reading ability. The methamphetamine group exhibited higher rates of neuropsychological impairment in most brain regions tested. Among methamphetamine users, neuropsychologically normal and impaired subjects did not differ with respect to self-reported age at first use, total years of use, administration route, or length of abstinence. Those with motor impairment had significantly greater methamphetamine use in the previous year, but impairment in cognitive domains was unrelated to methamphetamine exposure. The apparent lack of correspondence between substance use parameters and cognitive impairment suggests the need of further research into individual differences in vulnerability to the neurotoxic effects of methamphetamine.

van der Plas and co-workers (102) compared the performance of alcohol-, cocaine-, and methamphetamine-dependent individuals (men and women) with sex-matched healthy comparisons on complex decision-making, as measured, among others, by working memory, cognitive flexibility, and response inhibition. Methamphetamine-dependent individuals were impaired on complex decision-making, working memory, and cognitive flexibility, but not in response inhibition. Interestingly, decision-making was significantly more impaired in women addicted to methamphetamine than in men addicted to this drug. These findings suggest that executive functioning differs depending on the drug of choice and gender.

Moreover, Heaton and co-workers (103) found that HIV-positive methamphetamine users had more severe loss of interneurons, which was associated with cognitive impairment. Compared with other markers, loss of calbindin and parvalbumin interneurons in the frontal cortex was the most significant correlate to memory deficits.

In humans, there have been a number of studies showing impairment of working memory following MDMA use, especially in heavy and chronic recreational users (104, 105).

Results from Kuypers and Ramaekers' (106) study showed that a single dose of 75 mg of MDMA caused impairment of immediate and delayed recall on a verbal learning task during the intoxication phase. However, there was no residual memory impairment during the withdrawal phase.

Most of the neuropsychological disorders found in individuals who take ecstasy on a regular basis can be explained by the selective neurodegeneration processes that the drug appears to produce in hippocampal serotonin terminals (107). Moreover, the memory deficits of MDMA users are not only the result of a temporal or hippocampal dysfunction but also of a dysfunction of regions within the frontal cortex (108).

Although cognitive impairments induced by MDMA in humans have been linked to serotonin neurotoxicity, it remains unclear whether these impairments are due to the use of MDMA or other drugs. Hanson and Luciana (109) measured neurocognitive functioning in a sample of abstinent polydrug users with diverse MDMA habits and healthy non-drug-user controls. The results from this study suggest that moderate MDMA use does not lead to persistent impairments, but polydrug use (particularly in conjunction with cannabis) causes dose-related temporal and frontoparietal dysfunction.

MDMA users showed reduced serotonin transporter binding in multiple brain regions. Memory performance in the aggregate subject population was correlated with serotonin transporter binding in the dorsolateral prefrontal, orbitofrontal, and parietal cortex, all brain regions implicated in memory function. Prior exposure to MDMA significantly diminished the strength of this relationship (110). Reduced serotonin transporter availability might be a transient effect of heavy ecstasy use since this parameter partially recovered as the users reduced their MDMA consumption (111).

Serotonin transporters are key elements in the regulation of synaptic serotonin transmission and may be important to control for the potential covariance effect of a polymorphism in the serotonin transporter promoter gene region (5-HTTLPR) when studying the effects of MDMA as well as cognitive

functioning. Reay et al. (112) studied the effects of moderate and heavy MDMA use on cognitive function, as well as the effects of long-term abstention from MDMA in subjects genotyped for 5-HTTLPR. These authors concluded that the use of 'moderate' amounts of MDMA is not associated with impaired memory functioning, but heavy use of this substance may lead to long-lasting memory impairment. No effect of 5-HTTLPR or gender on memory function or MDMA use was observed.

Although an association between impairments in memory performance and a history of recreational ecstasy have also been corroborated (105), a number of methodological difficulties continue to hamper research in this field, the most important being the concomitant use of other illicit drugs. In particular, cannabis intake is prevalent among ecstasy users, and this combination produces a more deleterious effect on memory than either drug alone (104).

The interactions between MDMA and cannabis are complex: cannabis use is a well-recognized risk factor for neuropsychiatric disorders and it contributes to psychological problems and cognitive failures in ecstasy users. However, at the cellular level, cannabinoids have neuroprotective actions and partially block MDMA-induced neurotoxicity in laboratory animals (113).

Lamers et al. (114) compared the behavioural performance of MDMA/tetrahydrocannabinol (THC, the psychoactive compound from cannabis) users, with THC users and non-drug users matched for age and intellect. Results from this study demonstrate that THC users were impaired in some cognitive abilities to the same degree as MDMA/THC users, thereby suggesting that a certain degree of cognitive impairment attributed to MDMA is probably due to concurrent THC use.

It is important to highlight the paper by Halpern and co-workers (115). The major strength of that study was the inclusion of a unique group of MDMA users who, unlike MDMA users in other studies to date, had minimal or no exposure to other drugs. The authors concluded that the presence of residual cognitive deficits, even among unusually 'pure' frequent users of illicit MDMA, supports the notion that MDMA itself, rather than some associated factor, is responsible for the deficits observed.

In addition, working memory processing in ecstasy users has been shown to be associated with neural alterations in hippocampal and/or cortical regions, as measured by functional magnetic resonance imaging. Using functional imaging and a face-learning task, Roberts and co-workers (116) examined neural correlates of encoding and recalling face-name associations in recreational drug users whose predominant drug was ecstasy and in controls. Ecstasy users performed significantly worse in learning and memory compared with controls and cannabis users. Ecstasy-specific hypoactivity was evident in the right dorsal anterior and left posterior cingulated cortex. In the ecstasy plus cannabis group, brain activation was decreased in the right medial frontal, left parahippocampal, and left dorsal cingulate gyrus, and left caudate. These results elucidated ecstasy-related deficits, only some of which might be attributed to cannabis use.

It is claimed that binge use of MDMA boosts its subjective effects and sustains its actions over time (89). Schilt and co-workers (117) carried out a prospective cohort study in subjects taking a low dose of ecstasy (mean cumulative dose, 3.2 tablets) and did not find any effect of this substance on neurocognitive functions other than verbal memory. Similarly, Verbaten (118) performed a quantitative meta-analysis on the chronic effects of ecstasy use on working memory, assumed to consist of a central executive and four executive subcomponents: updating, attention shifting, inhibition, and access to long-term memory. This author did not detect a significant influence of ecstasy consumption on any of these subcomponents.

In contrast, a classical meta-analysis performed by Kalechstein et al. (119) concluded that MDMA use is associated with neurocognitive deficits. In the 11 studies that meet the relatively stringent inclusion/exclusion criteria for this meta-analysis, MDMA use was associated with neurocognitive deficits in each domain. Similarly, in the 23 studies with the relatively inclusion/exclusion criteria, the same result was found.

Furthermore, prospective memory involves remembering to execute a particular behaviour at some future point in time, which may be in the short or long term, for example, remembering to turn off the lights when leaving a room or remembering to attend a meeting, meet a friend, or pass on a message (120). A more up-to-date test battery that is sensitive to individual differences, both within clinical and normal populations, is the Cambridge Prospective Memory Test (121, 122). On the event-based prospective memory measure, ecstasy/polydrug users were impaired relative to both cannabis-only and non-users of illicit drugs. This group was also impaired compared with non-users on the time-based measure.

While deficits in aspects of prospective memory are evident among ecstasy/polydrug users, it is less clear which illicit drug or drugs are responsible for these deficits. It is striking that when the use of other drugs is controlled through partial correlation, no aspect of ecstasy use is statistically significant as a predictor of prospective memory performance. Relative to both drug-naive individuals and cannabis-only users, ecstasy/polydrug users performed significantly worse on both event-based and time-based prospective memory tasks.

Finally, memory impairment is prevalent in multiple sclerosis patients, but no drugs have been approved to treat these memory problems. Very recently, Sumowski et al. (123) conducted a re-analysis of a previously published clinical trial in which multiple sclerosis patients were randomly assigned to treatment (L-amphetamine or placebo) in a 4-week, double-blind, parallel-group, dose titration trial. Among memory-impaired patients, memory improved about 48.5% for those on L-amphetamine, but only by 1.0% for those on placebo. The L-isomer may have equivalent cognition enhancement with less adverse effects as a result of decreased potency in subcortical areas.

Morrow et al. (124) assessed the safety and efficacy of L-amphetamine for the treatment of cognitive dysfunction in multiple sclerosis. This was a 2:1 randomised, placebo-controlled, double-blind trial, involving 151 clinically definite multiple sclerosis patients with documented cognitive dysfunction. Five patients (four from the treatment group, one placebo) withdrew because of intolerable adverse events. L-Amphetamine was associated with improved learning and memory and was well tolerated in this study. However, because the positive findings were observed on secondary outcome measures, the study requires replication before L-amphetamine can be recommended for the treatment of cognitive impairment in multiple sclerosis.

In conclusion, the administration of amphetamine derivatives to laboratory animals and also their recreational ingestion by humans involve a series of cognitive adverse effects. These effects are the result of long-term neurotoxicity in which several receptors may be involved, the most important being dopaminergic and serotonergic receptors. Much research effort has been devoted to develop new methods and paradigms, using laboratory animals, to elucidate the pathways involved in memory disorders. Molecular biology has also contributed to a better understanding of the molecular mechanisms that are disrupted in memory and learning impairment. However, in spite of these advancements, we do not fully understand the addiction biology and the changes that occur in an addicted brain. Many studies and laboratories around the world are focusing on providing evidence about the molecular mechanisms of cognitive deficits induced by amphetamines. Recent publications demonstrate that addiction to amphetamine derivatives is a complex phenomenon in which many biochemical pathways become altered, thus producing this neurocognitive impairment.

Acknowledgments

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