

Clinical neuroscience of amphetamine-type stimulants: From basic science to treatment development

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Abstract

Abuse of amphetamine-type stimulants (ATS) poses a significant public health concern with known neurotoxic and neurocognitive effects to the user. In this chapter, we seek to integrate the latest research on ATS, particularly methamphetamine, by covering areas of pharmacology, neurocognitive effects, and the treatment of ATS use disorders with the goal of advancing the clinical neuroscience of ATS and highlighting avenues for future research.

Keywords

Amphetamine, Stimulants, Methamphetamine, Addiction, Clinical neuroscience, Treatment, ATS use disorders

1 INTRODUCTION

Amphetamine-type stimulants (ATS), including amphetamine, dextroamphetamine (D-amphetamine), methamphetamine, and amphetamine-like drugs such as methylphenidate, have a long history of use in the United States (U.S.) and continue to pose a significant public health concern in the U.S. and worldwide. Synthetic amphetamine was first popularized in the U.S. in the 1930s as an over-the-counter nasal decongestant and was used to reduce fatigue and suppress appetite during World War II. In the 1950s and 1960s, amphetamine was commonly prescribed as a medication for depression and obesity, with approximately 31 million prescriptions filled in the U.S. in 1967 (Anglin et al., 2000). Shortly thereafter, legislation was passed in

attempt to restrict the availability of amphetamine, and medicinal use began to decline (Gonzales et al., 2010); however, this reclassification of amphetamine to a more restrictive schedule led to a surge in illicit manufacturing and use of methamphetamine. Furthermore, the relatively recent increase in attention deficit hyperactivity disorder diagnoses has been accompanied by a resurgence of prescriptions for stimulant medications with diversion of these medications a growing concern for the nation (Rabiner, 2013). Despite multiple legislative attempts to limit public access, illicit ATS use remains highly prevalent.

Currently, ATS are the second most commonly used class of illicit drugs worldwide (UNODC, World Drug Report 2012); approximately 0.7% of the global population (33.8 million people) aged 15–64 years old reported using an ATS in 2010 (UNODC, World Drug Report 2013). In the U.S., estimates from 2013 suggest over 21.7 million people ages 12 years and older (8.3% of total responders) have used ATS for nonmedical purposes in their lifetimes, 3.5 million people (1.3%) reported past year use, and approximately 1.4 million (0.5%) of those identified as past month users. Further, 12 million (4.7%) of the individuals surveyed reported lifetime use of methamphetamine specifically, with approximately 440,000 (0.2%) of those identified as past month users (Substance Abuse and Mental Health Services Administration (SAMHSA), 2013a). Importantly, these estimates appear to be growing both in terms of supply and demand (UNODC, 2013).

Subsequently, the prevalence of ATS use disorders is also on the rise. In 2012, 535,000 (0.2%) individuals were estimated to meet the *Diagnostic and Statistical Manual of Mental Disorders* (4th ed., DSM-IV; American Psychiatric Association, 1994) criteria of ATS abuse or dependence, a significant increase from the 329,000 (0.1%) in 2011 (SAMHSA, 2013a). This increase was especially pronounced among individuals aged 18–25 years, with 0.5% meeting criteria in 2012, up from 0.3% in 2011. Furthermore, primary methamphetamine/amphetamine treatment admissions were more likely than all drug treatment admissions combined to receive long-term rehabilitation/residential treatment (16% vs. 7%) (SAMHSA, 2013b), suggestive of the exceedingly high costs associated with the treatment of ATS use disorders and underscoring the need for more efficacious, cost effective, and easily deliverable treatments.

Developing a greater understanding of the clinical neuroscience underlying the consequences of ATS use is an important step toward the development of more efficacious treatments for ATS use disorders. This is especially important with respect to medications development given the lack of any current FDA-approved medications for ATS dependence. Significant advances in preclinical and clinical research have begun to identify the neurochemical pathways affected by ATS use and highlight potential targets for intervention. Thus, knowledge of the pharmacological and neurological adaptations associated with ATS use could lead to the development of more efficacious medications and further inform psychosocial interventions for ATS use disorders (Table 1).

Given that methamphetamine is the most frequently used ATS worldwide (UNODC, 2013), and that studies of neurodegeneration, neurocognitive functioning,

Table 1 Chapter Highlights

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- Amphetamine-type stimulants (ATS) are the second most commonly used class of illicit drugs worldwide and the prevalence of ATS use disorders are on the rise
 - ATS have pervasive, and potentially long-lasting effects on the dopaminergic, noradrenergic, serotonergic, and opioidergic neurotransmitter systems throughout the brain and can result in detrimental effects to cognitive processes in heavy users
 - More efficacious treatment options, such as FDA-approved pharmacotherapies, are greatly needed for ATS use disorders
 - Promising medications currently under study for the treatment of ATS use disorders include oxytocin, bupropion, mirtazapine, topiramate, modafinil, and naltrexone
 - The integration of basic neuroscience and treatment development research could improve clinical outcomes in ATS use disorders by facilitating targeted treatment approaches
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and treatment most commonly target methamphetamine using populations, the majority of this chapter presents the current understanding of the clinical neuroscience behind methamphetamine use and associated disorders, expanded to ATS more broadly where applicable.

2 PHARMACOLOGY AND NEUROTOXICITY

As with most ATS, methamphetamine stimulates the release, and partially blocks the reuptake, of newly synthesized catecholamines in the CNS (Cho and Melega, 2002). Due to its structural similarity, methamphetamine interacts with the dopamine transporter (DAT), noradrenaline transporter (NET), serotonin transporter (SERT), and vesicular monoamine transporter-2 (VMAT-2) and reverses their endogenous function, thereby redistributing monoamines from storage vesicles into the cytosol. This process results in the release of dopamine, noradrenaline, and serotonin into the synapse, which then stimulate postsynaptic monoamine receptors (Cruickshank and Dyer, 2009). Methamphetamine also attenuates the metabolism of monoamines by inhibiting monoamine oxidase (Sulzer et al., 2005), further enabling the buildup of excess monoamines in the synapse.

The monoamines released due to the presence of ATS act on the major noradrenergic, serotonergic, and dopaminergic pathways of the brain. The medial basal forebrain, the hippocampus, as well as the prefrontal cortex (PFC) represent noradrenergic regions of interest for ATS effects, with various affected functions related to arousal, memory consolidation, and cognitive processing, respectively (Berridge and Waterhouse, 2003). Affected serotonergic neurons are dispersed throughout the brain, regulating diverse functions such as respiration, pain perception, sexual drive, reward, and higher-order cognitive processing (Hornung, 2003). In the case of dopamine, methamphetamine activates the mesolimbic, mesocortical circuit, and the nigrostriatal pathways, which have been related to the euphoric effects observed immediately after the ingestion of the drug (Homer et al., 2008).

Although no differences in striatal dopamine release between amphetamine and methamphetamine are observed (Melega et al., 1995), amphetamine is thought to result in a slightly greater dopamine release in the PFC, which may be responsible for the subtle differences between these drugs on behavioral tolerance and working memory measures (Shoblock et al., 2003a,b).

Repeated exposure to moderate to high levels of methamphetamine has been related to neurotoxic effects on the dopaminergic and serotonergic systems, leading to potentially irreversible loss of nerve terminals and/or neuron cell bodies (Cho and Melega, 2002). Preclinical evidence suggests that D-amphetamine, even when administered at commonly prescribed therapeutic doses, also results in toxicity to brain dopaminergic axon terminals (Ricaurte et al., 2005). Although the precise mechanisms remain unclear, the culmination of evidence suggests that the high level of cytoplasmic dopamine released as a result of ATS use leads to the accumulation of reactive oxygen species and severe oxidative stress on the neuron (Berman et al., 2008). Furthermore, frequent use of methamphetamine has been associated with reductions in striatal D₂-receptor availability (Groman et al., 2012; Volkow et al., 2001a), VMAT-2 density (Johanson et al., 2006), SERT density (Sekine et al., 2006), and DAT site density (McCann et al., 1998; Villemagne et al., 1998; Volkow et al., 2001b,c), with some markers (i.e., DAT density) showing improvement following prolonged (greater than 12 months) abstinence (Volkow et al., 2001b). Reduced markers of neuronal integrity and increased markers of glial content are also observed in chronic methamphetamine abusers, possibly indicating the proliferation of glial cells following neural damage (Chang et al., 2007; Ernst et al., 2000).

The potentiation of dopaminergic neurotransmission within the mesocorticolimbic circuit is thought to underlie the reinforcing properties of drugs of abuse, although evidence is accumulating on a converging role of the endogenous opioid systems in the establishment of reinforcement (Boutrel, 2008). In terms of neuroanatomy, endogenous opioid receptors are widely distributed throughout the CNS, with differential distributions per opioid receptor type. Importantly, opioid receptors and peptides are highly expressed in brain areas involved in reward and motivation, such as the ventral tegmental area (VTA) and nucleus accumbens (NAcc) (Mansour et al., 1995). Administration of classical exogenous opioids facilitates dopamine release in the mesolimbic reward system by activating μ - and δ -opioid receptors in the NAcc (Hirose et al., 2005; Murakawa et al., 2004) and by decreasing GABA-inhibition via μ - and κ -opioid receptors, which are mainly located on GABA interneurons in the VTA (Bonci and Williams, 1997; Shoji et al., 1999). Many nonopioid drugs of abuse, including ATS, are also known to interact with the endogenous opioid system (for a review, see Trigo et al., 2010), and this interaction may mediate some of the rewarding properties associated with acute ATS use (Boutrel, 2008). For example, acute amphetamine administration has been linked with increased β -endorphin levels in the NAcc (Olive et al., 2001), increased striatonigral dynorphin-like immunoreactivity (Bustamante et al., 2002; Hanson et al., 1988), and changes in the endogenous opioid mRNA expression in the striatum (Hurd and Herkenham, 1992; Smith and

McGinty, 1994; Wang and McGinty, 1995). Further, preclinical data suggest that the endogenous opioid system is involved in the induction and expression of methamphetamine-induced behavioral (locomotor) sensitization (Chiu et al., 2006), analogous to compulsive drug-seeking behavior in humans (i.e., drug craving; Itzhak and Ali, 2002), through its modulatory actions of the mesolimbic dopamine system (Ford et al., 2006).

In summary, methamphetamine and other ATS have pervasive and potentially long-lasting effects not only on the dopaminergic system but also on noradrenergic, serotonergic, and opioidergic neurotransmitter systems throughout the brain. It is through the culmination of these complex neurochemical modulations that significant behavioral and cognitive changes result.

3 NEUROCOGNITIVE EFFECTS

Many ATS are used therapeutically to improve attention and cognition; however, a review of the literature suggests dosage, and route of administration is a key determinant of the cognitive effects of these drugs (see Wood et al., 2014). Wood et al. (2014) argue that cognitive effects of ATS, including prescription medications such as D-amphetamine and methylphenidate, follow an inverted U dose–response curve, such that high doses result in detrimental effects on cognitive processing in domains such as learning and memory. In fact, a recent study of frequent recreational users of D-amphetamine observed impairments in performance on executive functioning and memory consolidation tasks, in addition to a trend toward reduced striatal DAT site binding and a blunted hemodynamic response to methylphenidate challenge, when compared to healthy controls (Schouw et al., 2013).

Chronic methamphetamine use, more specifically, has been associated with alterations across a broad spectrum of neurocognitive processes, although differentiating preexisting deficits from methamphetamine-induced cognitive deficits poses significant challenges (Dean et al., 2013), and concerns regarding the interpretation of these discrepancies and their clinical significance have been raised (Hart et al., 2012). The culmination of evidence acquired through various methodologies (e.g., preclinical, cross-sectional human, and brain imaging studies), however, supports the assertion that methamphetamine abuse does indeed cause cognitive decline in at least some individuals (i.e., individuals at the age of early-to-middle adulthood), and that individual difference factors such as education level and genotype further moderate this relationship (Dean et al., 2013). Cognitive domains including episodic memory, complex information processing speed, executive functions (e.g., response inhibition, novel problem solving), and psychomotor functions appear to be most affected in individuals with methamphetamine use disorders, with smaller, yet significant, effects also observed on measures of attention/working memory, language, and visuoconstruction (Scott et al., 2007).

A number of these cognitive discrepancies and other behavioral changes associated with methamphetamine abuse have been related to methamphetamine-induced

alterations in neurotransmission, such as memory deficits and impaired psychomotor coordination associated with reduced DAT site density (Volkow et al., 2001c), and increased aggression associated with reduced SERT density (Sekine et al., 2006). Further, preclinical evidence suggests D₂-specific alterations of the dopaminergic system may subserve some of the disturbances in learning observed with repeated methamphetamine use. Specifically, using a reversal learning task and PET in a pre-clinical sample of vervet monkeys given a chronic, escalating-dose regimen of methamphetamine revealed associations between the change in response to positive feedback and individual differences in the change in dopamine D₂-like receptor availability in the striatum, assessed pre- and postmethamphetamine regimen (Groman et al., 2012).

Functional neuroimaging procedures have begun to identify region-specific alterations in glucose metabolism and blood-oxygen-level-dependent measures of brain activation associated with these potentially affected cognitive processes. For example, glucose metabolism in the anterior and middle cingulate gyrus and the insula was negatively correlated with error rates on an auditory vigilance task indexing attentional processing in recently abstinent (4–7 days) methamphetamine abusers (London et al., 2005). Evidence also suggests frontal and insular involvement in learning and cognitive control changes associated with methamphetamine abuse. On a color-word Stroop task administered during functional magnetic resonance imaging, methamphetamine abusers display reduced reaction time (RT) adjustments and reduced PFC activity following conflict (i.e., incongruent) trials (Salo et al., 2009, 2013), and reduced RT, increased error rate, and reduced activation of the right inferior frontal gyrus (IFG), supplementary motor cortex/anterior cingulate gyrus, and the anterior insular cortex during the incongruent condition (Nestor et al., 2011).

Region-specific alterations in brain activation have also been observed on decision-making tasks in methamphetamine abusers. Methamphetamine abusers displayed reduced activation in the right IFG and the left medial frontal gyrus during a two-choice prediction task (where only 50% of the responses are reinforced with a correct response outcome), and a decrease in dorsolateral PFC (dlPFC) and right orbitofrontal cortex (OFC) activity in the active compared to control conditions, as opposed to the increase of activation in these areas observed in the healthy controls (Paulus et al., 2002). In a follow-up study using the same task, recently abstinent (average 25 days) individuals with methamphetamine dependence displayed reduced activation of the OFC, dlPFC, anterior cingulate cortex (ACC), and parietal cortex irrespective of the outcome, and attenuation of specific “success-related” patterns of brain activation as compared to healthy controls (Paulus et al., 2003). Furthermore, the degree of activation in the right middle frontal gyrus, middle temporal gyrus, and posterior cingulate during the two-choice prediction task in early remission (3–4 weeks abstinent) was predictive of relapse during a 1-year follow-up (Paulus et al., 2005).

On a temporal discounting task indexing reward-related decision-making, contrasting “hard choices,” where roughly equivalent preference is obtained for the immediate and delayed reward choices, and “easy choices,” in which the choices differ dramatically in value and preference, revealed less activation in the precuneus, right

caudate nucleus, ACC, and dlPFC in recently abstinent (2–8 weeks) individuals with methamphetamine dependence (Hoffman et al., 2008), and less activation of the left dlPFC and right intraparietal sulcus in active methamphetamine abusers (Monterosso et al., 2007), as compared to healthy controls. Furthermore, methamphetamine-dependent individuals undergoing treatment display disrupted risk-related processing, a component of decision-making, on the Risky Gains Task in both the ACC and insula (Gowin et al., 2013).

In summary, ATS abuse is associated with specific task-related behavioral and neural processing differences across a number of cognitive domains, which appear to be moderated by dose, route of administration, and other individual difference variables. Importantly, evidence is accumulating to suggest some of these differences are associated with altered dopaminergic processing (Groman et al., 2012) and clinically meaningful outcomes (Paulus et al., 2005), suggestive of a functional role for these cognitive differences in the development and maintenance of methamphetamine addiction.

4 TREATMENT

At present, few effective options exist for individuals seeking treatment for ATS use disorders, and to date, these options have been limited to psychosocial interventions. A systematic review of cognitive and behavioral treatments as applied specifically to methamphetamine use disorders concluded that good clinical outcomes are achieved with cognitive behavioral treatment (CBT; with and without motivational interviewing [MI]) and contingency management (CM) therapies involving the systematic use of reinforcement (Lee and Rawson, 2008). A number of caveats must be considered when interpreting these conclusions, however, such as the durability of treatment effects (especially with respect to CM programs). Furthermore, the effectiveness of psychosocial interventions is compromised by poor rates of treatment induction and retention (Shearer, 2007), and methamphetamine-related cognitive deficits in executive functioning, particularly those related to inhibitory control, have been hypothesized to potentially render heavily cognitive-based treatments ineffective (Baicy and London, 2007).

Given these important caveats of psychosocial interventions, and the heavy focus on the neurobiology of methamphetamine dependence, attention has shifted to the development of efficacious pharmacotherapies for methamphetamine addiction (NIDA, 2005). At present, no medication is approved by the U.S. Food and Drug Administration (FDA) for use in ATS use disorders. Numerous classes of medications are currently under study for methamphetamine use disorders, primarily in small clinical trials (for a recent focused review, see Brensilver et al., 2013). Some of the most promising medications include bupropion, mirtazapine, topiramate, modafinil, and naltrexone.

Bupropion, commonly prescribed as an antidepressant or smoking-cessation agent, is known to affect several biological targets. Widely described as a dopamine

and norepinephrine reuptake inhibitor (Stahl et al., 2004), bupropion also acts as a noncompetitive antagonist of several neuronal nicotinic acetylcholine (nACh) receptors (Slemmer et al., 2000). Clinical use of bupropion has been associated with reduced use of methamphetamine among baseline light, but not heavy, methamphetamine users (identified in a *post hoc* analysis; Shoptaw et al., 2008); however, its precise mechanism of action remains unclear.

In a 12-week trial, mirtazapine, a noradrenergic and specific serotonergic antidepressant, combined with CBT/MI counseling has also been associated with significant reductions in methamphetamine use (percent positive urines at the week 12 visit) in a sample of methamphetamine-dependent men who have sex with men (Colfax et al., 2011). The clinical efficacy of this agent may be related to its ability to enhance of the release of norepinephrine and 5-HT_{1A}-mediated serotonergic transmission (Anttila and Leinonen, 2001).

Topiramate, a sulfamate fructopyranose derivative and anticonvulsant, has been associated with reductions in methamphetamine use in large multisite clinical trial; however, no effects on total abstinence (negative urines during 6–12-week follow-up) were observed (Elkashef et al., 2012). Further analysis of this data identified a small subgroup of patients who exhibited consistent reductions of use or achieved abstinence during follow-up which were associated with topiramate treatment. This subgroup consisted of individuals who were more likely to have discontinued methamphetamine use (i.e., have a negative last urine) during the week prior to randomization (Ma et al., 2013) suggesting that topiramate may function best for relapse prevention. GABAergic modulation may be one possible mechanism underlying the potential efficacy of topiramate for methamphetamine treatment. Topiramate is known to facilitate GABAergic function via enhancement of inhibitory GABA_A-mediated currents at nonbenzodiazepine sites on the GABA_A receptor (White et al., 2000). Topiramate also antagonizes glutaminergic activity through an effect at kainate/alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid receptors (Gryder and Rogawski, 2003). Through these processes, topiramate is thought to modulate cortico-mesolimbic dopaminergic activity (Johnson, 2004), potentially stabilizing this activity and subsequently helping to prevent relapse or reduce methamphetamine use.

Cognitive-enhancing medications such as modafinil, an analeptic drug with known cognitive-enhancing properties, have garnered recent attention given the known cognitive deficits associated with chronic methamphetamine use (e.g., Ghahremani et al., 2011). Modafinil combined with CBT was associated with reduced methamphetamine use within a small sample of HIV+ gay men dependent on methamphetamine (McElhiney et al., 2009), although recent trials have not found strong support for a direct effect of modafinil on abstinence outcomes (e.g., Anderson et al., 2012; Heinzerling et al., 2010). The mechanism of action of modafinil is complex, involving multiple neurotransmitter systems, but its potential effects on ATS use may be related to inhibition of catecholamine transporters (Madras et al., 2006; Volkow et al., 2009), thereby increasing extracellular dopamine and norepinephrine levels.

Lastly, naltrexone, an opioid antagonist with greatest affinity for the μ - and κ -opioid receptors in humans (Emmerson et al., 1994; Toll et al., 1998), has been associated with reduced amphetamine use and greater abstinence rates in a sample of amphetamine-dependent individuals (Jayaram-Lindstrom et al., 2008). Further, amphetamine dependent patients with high levels of naltrexone (≥ 2 ng/ml) in their blood were 2.27 times more likely to be abstinent than patients with low naltrexone blood levels (< 2 ng/ml; Grant et al., 2010). Naltrexone-related reductions of cue-induced craving and subjective responses to methamphetamine administration have recently been observed in nontreatment seeking individuals with methamphetamine use disorders (Ray et al., 2015), advancing naltrexone as a potential treatment for methamphetamine addiction as well. The blockage of ATS-induced dopamine release in the mesolimbic dopamine system has been proposed as the neural mechanism underlying naltrexone's effects on craving and subjective reward (Ashenhurst et al., 2012; Benjamin et al., 1993; Jayaram-Lindstrom et al., 2004; Lee et al., 2005; Naleid et al., 2005; Widdowson and Holman, 1992) which may underlie the observed attenuation of ATS use.

In summary, the clinically limiting caveats of psychosocial treatments have engendered a strong interest in medication development for the treatment of ATS use disorders. A number of medications are currently under study in clinical research for the treatment of ATS use disorders, many with promising preliminary results. Pre-clinical research is also continuously advancing novel pharmacological agents that may progress to human trials for ATS use disorders. For example, oxytocin, a mammalian neuropeptide, has shown promise in reducing responding for intravenous methamphetamine in rodent models (Carson et al., 2010; Cox et al., 2013), which may one day translate to improved clinical outcomes associated with oxytocin treatment in humans. Treatment development for ATS use disorders has been a challenging enterprise, yet consistent with the addiction field broadly (Litten et al., 2012), efforts to refocus the field toward medications with novel therapeutic targets (e.g., the opioidergic system, cognitive enhancement) hold considerable promise for these complex disorders.

5 CONCLUSION AND FUTURE DIRECTIONS

Illicit ATS use continues to be highly prevalent despite numerous attempts to limit public access to the drugs and their precursors. Methamphetamine in particular is the most frequently used ATS worldwide and has the highest abuse potential, yet the diversion of stimulant medications is also a growing concern. Through actions on the brain's major dopaminergic, noradrenergic, serotonergic, and opioidergic pathways, repeated use of ATS (especially methamphetamine) is associated with significant neurotoxic effects and neurocognitive deficits, with only a few of such effects known to remediate following sustained abstinence. Thus, early identification of problematic ATS use and effective treatment implementation is critical to successful outcomes.

Advances in the identification of the neural pathways affected by ATS use have begun to highlight potential targets for intervention. The development of efficacious pharmacologic interventions is most promising in this regard, particularly given the profound neurochemical alterations associated with ATS use. Medications that act on the dopaminergic, GABAergic, and serotonergic systems have shown promise in reducing ATS use in clinical samples, and increasing evidence for the opioidergic system's role in the development of ATS use disorders has advanced pharmacologic agents targeting this pathway as plausible treatments.

By integrating basic neuroscience into treatment development research, one may elucidate how psychosocial and pharmacological interventions function to reduce ATS use and for whom specific interventions may be most efficacious. For example, the most effective medications may function via novel mechanisms such as enhancing the effectiveness of existent psychosocial interventions (e.g., via decreasing cognitive impairment) and by targeting intermediate phenotypes of addiction (e.g., relapse prevention/craving) (NIDA, 2005). Further, current research suggests that clinical outcomes may be improved by tailoring interventions to differences in patient presentation (e.g., heaviness of use, age of user, cognitive capability), some of which effects may be driven by individual differences in dopaminergic processing. Clinical neuroscience research is well positioned to address these questions and ultimately provide relief to thousands of individuals currently struggling to overcome their addiction to these stimulating and reinforcing drugs.

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