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Preclinical pharmacology of amphetamine: Implications for the treatment of neuropsychiatric disorders

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ABSTRACT

The primary mechanism by which amphetamine exerts its neurobehavioral effects is through an enhancement of synaptic monoamine levels, which is mediated by interactions with monoamine transporters, storage, and metabolism. However, preclinical data are now emerging that support more widespread neurobiologic effects for amphetamine. This review describes preclinical evidence suggesting that direct interactions of amphetamine with monoamine systems, which results in increased synaptic monoamine availability, has downstream effects on nonmonoaminergic systems, including glutamate, endogenous opioid, endocannabinoid, and acetylcholine systems. Furthermore, evidence suggests that amphetamine can modulate synaptic plasticity through modulation of glutamatergic systems, intracellular signaling cascades, and neurotrophic factor activity. Functional activity of these systems is implicated in the regulation of neurobehavioral processes that include cognition, mood, motivated behavior/hedonic processes/addiction, and arousal. As such, the ability of amphetamine to influence the function of systems that mediate these processes suggests amphetamine-based agents may have utility in the treatment of psychiatric disorders in which these systems and processes are dysfunctional. Amphetamine-based agents are currently approved by the US Food and Drug Administration only for the treatment of attention-deficit/hyperactivity disorder and narcolepsy. Preclinical and clinical research for amphetamine-based pharmacotherapy for other psychiatric disease states is examined. This should encourage further research on the preclinical pharmacology of amphetamine and its implications for the treatment of neuropsychiatric disorders.

Contents

Abbreviations: 5-HT, serotonin; ACh, acetylcholine; ADHD, attention-deficit/hyperactivity disorder; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; BDNF, brain-derived neurotrophic factor; CB, cannabinoid; CB_1, type 1 cannabinoid receptor; CB_2, type 2 cannabinoid receptor; CNS, central nervous system; DA, dopamine; D_1, dopamine receptor type 1; D_2, dopamine receptor type 2; DAT, dopamine transporter; Glu, glutamic acid or glutamate; $GluN_2B$, NMDA receptor subunit 2B; K_i, inhibitory binding constant; LTD, long-term depression; LTP, long-term potentiation; MAO, monoamine oxidase; MDD, major depressive disorder; mGluR, metabotropic receptor; mGluR5, metabotropic glutamate receptor type 5; MPEP, 2-methyl-6-(phenylethynyl)pyridinehydrochloride; mRNA, messenger RNA; NAcc, nucleus accumbens; NE, norepinephrine; NET, norepinephrine transporter; NMDA, N-methyl-D-aspartate; PPD, preprodynorphin; TrkB, tyrosine kinase B; VTA, ventral tegmental area.

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1. Introduction

Amphetamine is the prototypical psychostimulant, eliciting behavioral effects, such as increased arousal or wakefulness, decreased appetite, hyperactivity, perseveration, and, in humans, euphoria (Berman et al., 2009). A substantial body of evidence indicates that direct interactions of amphetamine with monoamine transporters, including the dopamine transporter (DAT) and the norepinephrine transporter (NET), result in increased synaptic availability of dopamine (DA) and norepinephrine (NE), respectively, through blockade of monoamine reuptake (Rothman & Baumann, 2006; Robertson et al., 2009). However, a growing body of evidence indicates that amphetamine also produces a wide array of neurobiologic effects on other neurotransmitter systems, presumably as a downstream consequence of its interactions with monoamine systems. These downstream effects may contribute to its overall neurobehavioral profile.

In view of the diverse range of amphetamine's central nervous system (CNS) actions, it may have more varied clinical applications than previously considered. For example, a Cochrane database review (Candy et al., 2008) reported that during the 1960s multiple studies investigated the therapeutic utility of psychostimulants, including amphetamine, for the treatment of major depressive disorder (MDD). However, interest in this clinical application waned, due to the abuse profile of amphetamine. Nevertheless, developing an appreciation for the diverse research relating to the complex preclinical pharmacology of amphetamine by means of a scientific literature review may help support its theoretical usage and reveal its potential effects on the pathophysiology and neurochemistry of psychiatric disorders, including attention-deficit/hyperactivity disorder (ADHD), narcolepsy, and augmentation therapy for MDD, negative symptoms and cognitive deficits of schizophrenia, and bipolar disorder.

This review (1) describes preclinical evidence pertaining to the diverse effects of amphetamine on multiple neurobiologic systems and processes (Table 1); (2) provides a summary of the systems involved and the neuropsychiatric disorders linked to dysfunction in these systems; and (3) discusses the potential clinical applicability of amphetamine in light of the current understanding of the neurobiologic underpinnings of various neuropsychiatric disorders.

Given the diverse methodologies and animal models employed across studies that have assessed the neurobehavioral effects of amphetamine, it is difficult to compare the sensitivity of these systems to the various effects of amphetamine. Table 2 summarizes the amphetamine doses reported to impact specific neurotransmitter systems. For the nonmonoamine systems, the effects of amphetamine are presumed to be indirect/downstream effects that are mediated, at least in part, by the direct activation of monoamine systems.

2. Dopaminergic system interactions

The primary DA pathways originate from neurons located in the midbrain and hypothalamus (Moore, 1987; Zahm & Trimble, 2008). Pathways that arise from midbrain DA neurons are the mesocortical and mesolimbic pathways, which include projections from the ventral tegmental area (VTA) to various cortical and subcortical structures, and the nigrostriatal pathway, which projects from the substantia nigra *pars compacta* to dorsal regions of the basal ganglia (Zahm & Trimble, 2008). The mesocortical and mesolimbic pathways are associated with an array of functions (reinforcement/hedonic processes, cognitive function and emotional control). Synaptic DA interacts with multiple DA receptors of which 5 subtypes have been identified (D_1 through D_5) and are located both presynaptically and postsynaptically (Baldessarini & Tarazi, 1996).

Alterations in dopaminergic activity in these pathways are implicated in multiple disorders, including ADHD, narcolepsy, bipolar disorder, drug abuse, MDD, and schizophrenia (Wisor et al., 2001; Miklowitz & Johnson, 2006; Heal et al., 2009; El Mansari et al., 2010; Shen et al., 2012). The nigrostriatal pathway plays a critical role in the programming and execution of movement (Zahm & Trimble, 2008), with the primary symptoms of Parkinson's disease being related to the profound degeneration of DA neurons in the substantia nigra *pars compacta* and the nigrostriatal pathway (Corti et al., 2011). The hypothalamic DA pathway (i.e., the tuberoinfundibular pathway) projects from the arcuate nucleus of the hypothalamus to the pituitary gland (Moore, 1987). In this pathway, DA receptors play an important role in controlling prolactin secretion (Moore, 1987; Bernichtein et al., 2010).

The primary mechanism of action of amphetamine when administered acutely is to enhance the extracellular concentrations of DA by blockade of DA reuptake. This effect is mediated by an inhibitory action at the DAT, the vesicular monoamine transporter 2 (which displaces DA from vesicular storage pools), and by the inhibition of monoamine oxidase (MAO) activity, which subsequently reduces cytosolic DA metabolism (Lu & Wolf, 1997; Heal et al., 2009; Sulzer, 2011). During the first few minutes of exposure, amphetamine induces a rapid increase in surface trafficking of DAT, a process which may be regulated by the β isozyme of protein kinase C (Chen et al., 2009). Furthermore, amphetamine not only enhances responses to phasically-released DA by inducing nonvesicular DA release via the DAT, but also augments phasic dopamine signaling by directly enhancing vesicular DA release (Daberkow et al., 2013). With longer durations of amphetamine exposure, a compensatory downregulation of the DAT has been reported (for review see (Vaughan & Foster, 2013)).

Both systemic and intrastriatal amphetamine administration increase DA efflux and decrease levels of the DA metabolites dihydroxyphenylacetic acid and homovanillic acid in the striatum of rats (Karoum et al., 1994; Miele et al., 2000). Amphetamine-induced DA efflux increases the level of occupancy of D_2 receptors, as evidenced by reduced DA receptor antagonist binding in the striatum of humans (Laruelle et al., 1996) and mice (Cumming et al., 2002). The importance of increased DA efflux in the behavioral effects of amphetamine is supported by evidence from genetic models. For example, in mice with decreased vesicular DA uptake and decreased striatal DA, amphetamine-stimulated motor activity is blunted (Robertson et al., 2009; Brunk et al., 2010). However, the administration of high doses of amphetamine can produce abnormal stereotypic behaviors in rodents, which is characterized by abnormal movements of the mouth, excessive sniffing, grooming, and rearing (Scholl et al., 2009; Doremus-Fitzwater & Spear, 2010; Enman & Unterwald, 2012).

3. Norepinephrine system interactions

The primary central NE pathways originate from cell bodies in the locus ceruleus, with ascending projections to diverse cortical, subcortical, and hypothalamic regions and descending projections to the spinal cord (Berridge & Waterhouse, 2003). Projections to the various forebrain regions are implicated in mediating aspects of cognitive function and drug abuse and may play a role in psychiatric disorders, such as ADHD, bipolar disorder, MDD, and schizophrenia (Berridge & Waterhouse,

Table 1
Brief overview of the central organization of the neurobiological systems affected by amphetamine.

	Organization[a]	CNS distribution[a]	Neurobiologic processes	Disease states associated with dysfunction
DA	•Receptors: D_1–D_5	•Cell bodies: substantia nigra *pars compacta*, ventral tegmental area, hypothalamus •Projection areas: amygdala, cortex, hippocampus, hypothalamus, pituitary gland, striatum, spinal cord	•Cognition (Berridge & Waterhouse, 2003; El Mansari et al., 2010) •Mood (Miklowitz & Johnson, 2006; El Mansari et al., 2010) •Motivated behavior/hedonic processes/addiction (Koob, 2006; Wee & Koob, 2010) •Behavioral arousal and fatigue (Datta & Maclean, 2007; Qu et al., 2010)	•ADHD, addiction, bipolar disorder, depression, and schizophrenia (Miklowitz & Johnson, 2006; Heal et al., 2009; El Mansari et al., 2010; Sulzer, 2011; Shen et al., 2012)
NE	•Receptors: $\alpha_{1(A,B,D)}$, $\alpha_{2(A,B,C)}$, β_1, β_2, β_3; α-receptors have multiple subtypes	•Cell bodies: locus ceruleus, lateral tegmentum •Primary projection areas: amygdala, brain stem, cortex, hippocampus, hypothalamus, spinal cord, striatum, thalamus	•Cognition (Berridge & Waterhouse, 2003; El Mansari et al., 2010) •Mood (Davidson, 2010) •Behavioral arousal and fatigue (Datta & Maclean, 2007)	•Addiction, bipolar disorder, MDD, and schizophrenia (Berridge & Waterhouse, 2003)
5-HT	•Receptor: 5-HT_1 through 5-HT_7, with several containing multiple subtypes	•Cell bodies: raphe nuclei (Charnay & Leger, 2010; Bello & Liang, 2011) •Projections: widespread into various regions of the forebrain, midbrain, and brain stem	•Mood (Cools et al., 2008; Davidson, 2010) •Motivated behavior/hedonic processes/addiction (Koob, 2006) •Behavioral arousal and fatigue (Datta & Maclean, 2007)	•Bipolar disorder, MDD, and schizophrenia (Millan, 2000; Miklowitz & Johnson, 2006; Engleman et al., 2008; Savitz et al., 2009)
Glu	•Receptors: NMDA, AMPA, kainate, mGluR; each has multiple subtypes	•Primary excitatory neurotransmitter in the brain, with a widespread distribution	•Cognition (Jay, 2003; Lisman et al., 2011) •Mood (Sanacora et al., 2012) •Motivated behavior/hedonic processes/addiction (Koob, 2006)	•Schizophrenia and MDD (Goldman-Rakic & Selemon, 1997; Mathews et al., 2012; Moghaddam & Javitt, 2012; Sanacora et al., 2012)
Opioids	•Receptors: δ-, κ-, μ-receptors; each has multiple subtypes	•Widely distributed across the olfactory tract, amygdala, cortex, striatum, hypothalamus, spinal cord, thalamus, brain stem, and periaqueductal gray	•Mood (Pradhan et al., 2011) •Motivated behavior/hedonic processes/addiction (Koob, 2006; Wee & Koob, 2010)	•Drug abuse and MDD (Le Merrer et al., 2009; Wee & Koob, 2010; Pradhan et al., 2011)
Cannabinoids	•Receptors: CB_1 and CB_2	•Basal ganglia, cortex, amygdala, and cerebellum	•Mood (Pertwee, 2009)	•Anxiety and affective disorders (Pertwee, 2009)
ACh	•Receptors: nicotinic, muscarinic; muscarinic receptors have multiple subtypes	•Cell bodies: mesopontine tegmentum, nucleus basalis, and septal nucleus •Projections: striatum, cortex, thalamus, basal forebrain, and hippocampus	•Cognition (Hasselmo, 2006; Dani & Bertrand, 2007; Dumas & Newhouse, 2011) •Mood (Philip et al., 2012) •Behavioral arousal and fatigue (Datta and Maclean, 2007)	•Schizophrenia and MDD (Olincy and Freedman, 2012; Philip et al., 2012)

5-HT_1 = serotonin receptor type 1; 5-HT_7 = serotonin receptor type 7; ACh = acetylcholine; ADHD = attention-deficit/hyperactivity disorder; AMPA = α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; CB_1 = cannabinoid receptor subtype 1; CB_2 = cannabinoid receptor subtype 2; DA = dopamine; MDD = major depressive disorder; mGluR = metabotropic glutamate receptor; NE = norepinephrine; NMDA = N-methyl-d-aspartate.
[a] Data from Iversen LL, Iversen SD, Bloom FE, Roth RE. *Introduction to Neuropsychopharmacology*. New York, NY: Oxford University Press; 2009; and Stahl SM. *Stahl's Essential Psychopharmacology*. 4th ed. Cambridge, UK: Cambridge University Press; 2013.

2003). Amphetamine increases synaptic availability of NE through mechanisms related to the blockade of the NET and inhibition of MAO type A (MAO-A) (Heal et al., 2009; Sulzer, 2011). After acute administration of amphetamine (0.5 mg/kg), DA and NE efflux in the nucleus accumbens and medial prefrontal cortex of the rat increases (Kleijn et al., 2012), leading to enhanced DA and NE neurotransmission in the limbic and cortical pathways.

4. Serotonergic system interactions

The primary serotonin (5-HT) pathways in the brain originate in the raphe nuclei; these pathways project rostrally to diverse cortical and subcortical regions and caudally to the spinal cord (Charnay & Leger, 2010; Bello & Liang, 2011). The various forebrain projections of the 5-HT system (i.e., frontal cortex, ventral striatum, hippocampus, and amygdala) are involved in cognitive function, mood, and psychiatric disorders (Millan, 2000; Miklowitz & Johnson, 2006; Savitz et al., 2009). The effects of 5-HT are mediated by receptors (of which there are at least 14 subtypes) located presynaptically and postsynaptically (Hayes & Greenshaw, 2011). Compared with its effects on the catecholamines, amphetamine produces only minimal increases in synaptically available 5-HT through weak blockade of the 5-HT transporter (Ritz et al., 1987; Ritz & Kuhar, 1989) and weak inhibition of MAO-A (Miller et al., 1980; Karoum et al., 1994).

The role of 5-HT systems in the behavioral effects of amphetamine has been reported in multiple studies. For example, administration of amphetamine increases motor activity to a lesser degree in mice with reduced serotonergic function compared with normal control mice (Innos et al., 2013). Furthermore, in mice lacking 5-HT_{1A} receptors, amphetamine-stimulated hyperlocomotion occurs in the absence of compensatory changes in DAT, D_1, or D_2 receptor—binding density (van den Buuse et al., 2011). However, data also suggest that the effects of amphetamine are mediated by interactions between 5-HT and DA systems, with the 5-$HT_{2A/2C}$ receptor antagonist ritanserin potentiating amphetamine-mediated DA efflux in the rat prefrontal cortex (Pehek & Bi, 1997) and the selective 5-HT_{2A} receptor antagonist SR 46349B reducing amphetamine-induced increases in DA efflux in rat striatum and nucleus accumbens (Porras et al., 2002).

5. Glutamatergic system interactions

Glutamic acid (glutamate; Glu) is the primary excitatory neurotransmitter in the brain. The CNS actions of Glu are mediated by metabotropic (mGluR) and ionotropic (N-methyl-D-aspartate [NMDA], α-

amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid [AMPA], and kainate) receptors (Orrego & Villanueva, 1993). Given its ubiquitous distribution throughout the brain, Glu has been implicated in cognitive functions, synaptic plasticity, nociception, excitotoxicity, and seizure generation and, as such, plays an important role in neuropsychiatric disorders, including MDD, bipolar disorder, and schizophrenia (Mathews et al., 2012; Moghaddam & Javitt, 2012; Sanacora et al., 2012).

Amphetamine influences a variety of Glu systems through multiple downstream mechanisms, including increased Glu efflux and changes in the expression of AMPA and NMDA receptors. In rats, amphetamine increases Glu efflux in the nucleus accumbens, striatum, and VTA (Xue et al., 1996; Miele et al., 2000; Rahman & Bardo, 2008). The increased Glu efflux in the nucleus accumbens associated with systemic amphetamine administration is prevented by systemic administration of the NMDA receptor antagonist MK-801 (Rahman & Bardo, 2008). In addition to increasing Glu efflux, amphetamine transiently increases cell surface expression of the Glu-R1 subunit of the AMPA receptor in the nucleus accumbens, which is considered a prerequisite for enhancing excitatory transmission (Nelson et al., 2009).

The NMDA receptor has also been implicated in mediating amphetamine's downstream effects. For example, the increases in striatal expression of the $GluN_2B$ subunit of the NMDA receptor in mice lacking the α-subunit of the Go2 GTPase (which exhibit decreased vesicular DA uptake and decreased striatal DA) partially contributed to the reduced amphetamine-stimulated motor activity that is observed in these mice (Brunk et al., 2010). Furthermore, in genetically modified mice with impaired NMDA function due to elimination of the serine racemase enzyme, the expression of behavioral locomotor sensitization to amphetamine is slowed and its magnitude is attenuated (Benneyworth & Coyle, 2012). In another genetic mouse model, in which partial reduction of the glycine GlyT1 transporter increased NMDA function, the acquisition of behavioral locomotor sensitization to amphetamine is more rapid (Benneyworth & Coyle, 2012). Following repeated exposure to amphetamine and subsequent withdrawal, intraVTA infusions of AMPA increase DA and Glu efflux in the nucleus accumbens, with the effect on Glu efflux being reversed by intra-accumbal antagonism of D_1 and D_2 receptors (Giorgetti et al., 2001).

Metabotropic Glu receptors (mGluRs) are also implicated in the effects of amphetamine. Acute amphetamine administration in rats produces transient changes in type 5 mGluR expression, with decreases observed in the striatum and increases observed in the medial prefrontal cortex (Shaffer et al., 2010). Amphetamine-associated increases in the phosphorylation of transcriptional regulators, such as cyclic adenosine monophosphate response element—binding (CREB) protein, in rats are blocked by systemic administration of the type 5 mGluR antagonist n-phenyl-7-(hydroxy imino)cyclopropa [b]chromen-1a-carboxamide (Choe et al., 2002). The type 5 mGluR antagonist, 2-methyl-6-(phenylethynyl)pyridinehydrochloride (MPEP) also enhances amphetamine-associated improvements in avoidance learning, stereotypic motor activity, and stereotypic rotational behavior in mice (Manago et al., 2013). However, the influence of mGluRs on the effects of amphetamine is not limited to type 5 mGluR. The type 2/3 mGluR agonist, LY35474, attenuates amphetamine-stimulated increases in locomotion and fine-motor movement and attenuates amphetamine-stimulated increases in DA in the striatum and nucleus accumbens of rats (Pehrson & Moghaddam, 2010). The type 2/3 mGluR agonist, LY35474, also attenuates amphetamine-stimulated locomotion in C57Bl/6J mice and in type 3 mGluR-deficient mice; a similar attenuation of amphetamine-stimulated locomotion is not observed in type 2 mGluR-deficient mice (Woolley et al., 2008). Furthermore, in transgenic mice lacking the type 1 mGluR, locomotor responses to amphetamine are enhanced (Mao et al., 2001). Collectively, these studies suggest a role for mGluRs in modulating the neurobehavioral effects of amphetamine.

6. Opioid system interactions

Endogenous opioid peptides (i.e., dynorphins, enkephalins, endorphins, endomorphins) and their receptors (δ, κ, and μ) are widely distributed throughout the brain (Le Merrer et al., 2009). Although there is substantial overlap in the distribution of opioid receptors, μ-receptors are most highly expressed in regions of the amygdala, thalamus, and brain stem; δ-receptors in the olfactory tract, amygdala, cortex, and striatum; and κ-receptors in regions of the anterior forebrain, striatum, and hypothalamus (Le Merrer et al., 2009). The central role of opioid systems in analgesia and drug abuse is well known (Wee & Koob, 2010; Raehal et al., 2011). However, studies also implicate opioid peptides in the regulation of emotional control (Pradhan et al., 2011), suggesting that they may also be involved in mood disorders.

Amphetamine administration induces changes in endogenous opioid systems. Thus, acute systemic amphetamine increases striatal messenger RNA (mRNA) expression of the opioid precursor peptides preprodynorphin and preproendorphin in rats (Wang & McGinty, 1996; McGinty et al., 2011) and of preproendorphin in mice (Saylor & McGinty, 2008). Repeated administration of amphetamine to rats also increases expression of the proto-oncogene cFos in enkephalin-positive neurons of the dorsal and ventral striatum (Mattson et al., 2007) indicating activation of those neurons. Furthermore, acute administration of amphetamine increases extracellular endorphin levels in the ventral striatum of rats (Olive et al., 2001) and, in the human brain, reduces [^{11}C]carfentanil binding (an index of endogenous opioid release) in the frontal cortex, basal ganglia, thalamus, anterior cingulate, and insular cortex (Colasanti et al., 2012). Interestingly, the change of [^{11}C]carfentanil binding potential in ventral striatum correlates with subjective ratings of euphoria (Colasanti et al., 2012). Administration of amphetamine also reduces κ-opioid receptor-mediated inhibition of Glu efflux in the ventral striatum of rats, presumably as a consequence of receptor desensitization resulting from DA-mediated dynorphin efflux (Xia et al., 2008).

The effects of amphetamine on endogenous opioid systems may be mediated in part through secondary pathways, which include brain-derived neurotrophic factor (BDNF), DA, and Glu (Olive et al., 2001; Xia et al., 2008; McGinty et al., 2011). For example, amphetamine-induced increases in striatal mRNA expression of preproenkephalin and preprodynorphin in rats are blocked by systemic administration of the D_1 receptor antagonist SCH 23390 (Wang & McGinty, 1996). Similarly, increased striatal expression of preprodynorphin is blocked by systemic administration of the D_2 receptor antagonist eticlopride (Wang & McGinty, 1996). These data suggest the effects of amphetamine on opioid systems are secondary to the release of striatal DA. However, as amphetamine-induced upregulation of striatal preprodynorphin mRNA expression in rats is also blocked by administration of the tyrosine kinase inhibitor K2542a (McGinty et al., 2011), the binding of BDNF to the tyrosine kinase B (TrkB) receptor may also be involved in the effects of amphetamine on endogenous opioid systems.

Opioid systems have also been shown to modulate the acute effects of amphetamine. In rats, administration of the δ-opioid agonist SNC80 enhanced amphetamine-stimulated striatal DA efflux at a dose that did not promote striatal DA efflux when administered alone (Bosse et al., 2008). Opioid modulation of amphetamine-induced behavior in the rat has also been demonstrated by the ability of naltrexone, an opioid receptor antagonist, to attenuate the reinstatement of amphetamine self-administration and amphetamine-stimulated locomotor activity (Haggkvist et al., 2009a,b). Consistent with this finding, administration of naltrexone attenuates the subjective effects of amphetamine on “feeling high” (measured on a visual analog scale) in healthy human volunteers (Jayaram-Lindstrom et al., 2004) and in individuals with amphetamine dependence (Jayaram-Lindstrom et al., 2008).

7. Cannabinoid system interactions

The two CB receptors, type 1 (CB_1) and type 2 (CB_2), are substrates for two endogenous compounds – N-arachidonoylethanolamine (also known as anandamide) and 2-arachidonoylglycerol – that serve as agonists (Howlett et al., 2011). High levels of cannabinoid (CB) receptors in the brain are found in the basal ganglia, cortex, amygdala, and cerebellum (Elphick & Egertova, 2001; Freund et al., 2003). Based on the distribution of CB receptors in the brain and the observed neurobehavioral effects of CB-active agents, the clinical relevance of this system has been discussed in terms of the regulation of movement disorders and affective disorders (Pertwee, 2009). The interaction of amphetamine with CB systems does not appear to be mediated by direct effects on CB receptors; rather, they are likely mediated through indirect interactions with DA and Glu systems (Huang et al., 2003; Tzavara et al., 2009; Kleijn et al., 2012).

Table 2
Overview of the interactions of amphetamine on various neurotransmitter systems.

System	Species	Dose/dosage[a]	Representative neurobiological effects of amphetamine
MAO inhibition			
	Rat	1–10 mg/kg (systemic)	•Inhibits MAO type A activity (Miller et al., 1980; Karoum et al., 1994)
		Not provided	•Binding affinities (K_i): MOA type A, 33.8 μM, MOA type B, 161 μM (Robinson, 1985)
DA			
	Mouse	0.1–2.5 mg/kg (systemic)	•Increases NAcc DA efflux (Tzavara et al., 2009)
			•D_1 knockout attenuates amphetamine-stimulated motor activity and locomotor sensitization (El-Ghundi et al., 2010)
			•D_1 antagonist (SCH23390) blocks amphetamine-facilitated LTP in prefrontal cortex (Xu et al., 2010)
			•Repeated exposure (4 d) increases striatal synaptosome D_1/D_2 ratio (Brunk et al., 2010)
	Rat	Not provided	•Binding affinity (K_i): DAT, 3.5 μM (Ritz and Kuhar, 1989)
		0.5–10 mg/kg (systemic)	•Reduces striatal DOPAC formation (Miller et al., 1980; Karoum et al., 1994)
			•Increases 3MT:DOPAC ratio in frontal cortex, hippocampus, and NAcc (Karoum et al., 1994)
			•Increases NAcc and medial prefrontal cortex DA efflux (Olsson et al., 2009; Kleijn et al., 2012)
			•Repeated exposure (4 d) increases whole brain DA content (Zhou et al., 2010)
			•Increases exocytotic DA release and blocks DA synaptic reuptake (Daberkow et al., 2013)
		2–100 μM (incubation)	•Increases whole brain synaptosomal DA release (Floor and Meng, 1996)
			•D_2 antagonists (haloperidol and sulpiride) block amphetamine-induced LTD in the lateral amygdala (Huang et al., 2003)
	Human	0.3 mg/kg (IV)	•Increases striatal DA release measured by reduced IBZM binding with SPECT (Laruelle et al., 1996)
NE			
	Mouse	0.1 mg/kg (systemic)	•β-adrenergic antagonist (propranolol) attenuates amphetamine facilitation of prefrontal cortex LTP (Xu et al., 2010)
	Rat	Not provided	•Binding affinities (K_i): NET, 0.82 μM; α_2-receptor, 2.37 μM; α_1-receptor, 52.78 μM; β-adrenergic, 90.76 μM (Ritz and Kuhar, 1989)
		0.5–2.5 mg/kg (systemic)	•Increases NAcc and medial prefrontal cortex NE efflux (Kleijn et al., 2012)
			•Repeated exposure (4 d) increases whole brain NE content (Zhou et al., 2010)
	Human	1–100 μM (incubation)	•Reduces NET expression in human embryonic kidney cells (Zhu et al., 2000)
			•Reduces cell surface expression of the NET in catecholamine cell stably transfected with the human NET (Dipace et al., 2007)
5-HT			
	Mouse	5.0 mg/kg (systemic)	•5-HT_{1A} knockout enhances amphetamine-stimulated motor activity (van den Buuse et al., 2011)
			•Increases 5-HT levels and decreases 5-HT turnover in dorsal striatum, mesencephalon, temporal cortex (Innos et al., 2013)
	Rat	Not provided	•Binding affinities (K_i): 5-HT-T, 10.5 μM (Ritz and Kuhar, 1989)
		0.5–2.5 mg/kg (systemic)	•Increases NAcc 5-HT efflux (Kleijn et al., 2012)
			•5-$HT_{2A/2C}$ receptor antagonist ritanserin potentiates amphetamine-mediated DA efflux in the rat prefrontal cortex (Pehek and Bi, 1997)
Glu			
	Mouse	0.5–5.0 mg/kg	•mGluR5 antagonist (MPEP) facilitates amphetamine-associated enhancements of passive avoidance learning and motor activity (Manago et al., 2013)
			•Increases cortical and decreases striatal mGluR5 receptor levels (Shaffer et al., 2010)
			•mGluR5 antagonist (MPEP) reverses hyporesponsiveness of CB_1-deficient mice to amphetamine-stimulated motor activity (Tzavara et al., 2009)
			•Repeated exposure (4 injections) increases striatal $GluN_2B$ subunit expression in $Go\alpha_2$ (α-subunit of the heterotrimeric G-protein Go2)–deficient mice (Brunk et al., 2010)
			•Repeated exposure (5 d) increases miR-181a expression (a microRNA associated with GluA2 subunit of AMPA receptor) in midbrain, prefrontal cortex, caudate putamen, and hippocampus (Saba et al., 2012)
			•mGluR 2/3 agonist (LY35470) attenuates amphetamine-stimulated locomotor activity in C57Bl/6J mice and in mGluR3-deficient mice, but not in mGluR2-deficient mice (Woolley et al., 2008)
			•mGluR1-deficient mice exhibit enhanced locomotor response to amphetamine (Mao et al., 2001)
	Rat	0.5–5.0 mg/kg	•Increases striatal and NAcc Glu efflux (Miele et al., 2000; Rahman and Bardo, 2008)
			•Increases striatal transcription factor and kinase expression attenuated by intrastriatal mGluR1/5 antagonist (PHCCC) and an mGluR5 antagonist (MPEP) (Choe et al., 2002; Manago et al., 2013)
			•Facilitates VTA DA cell firing stimulated by an mGluR 1/5 agonist (DHPG) (Ahn et al., 2010)
			•mGluR 2/3 agonist (LY35470) attenuates amphetamine-stimulated locomotion and DA increases in the striatum and NAcc (Pehrson and Moghaddam, 2010)
			•Repeated exposure (5 d) increases glutamate efflux in NAcc and VTA in response to intra-VTA administration of AMPA (Giorgetti et al., 2001)
			•Repeated exposure (4 d) decreases striatal NR2B subunit levels (Mao et al., 2009)
			•Repeated exposure (7 d) facilitates NMDA-mediated LTP in VTA DA neurons (Ahn et al., 2010)
			•Repeated exposure (4 d) increases whole brain Glu content (Zhou et al., 2010)
			•Repeated exposure (6 d) enhances amphetamine-stimulated NAcc and VTA Glu efflux (Xue et al., 1996)
			•Repeated exposure (12 d) increases striatal and cortical mGluR8 mRNA expression (Parelkar and Wang, 2008)
		Intracranial infusion (2 mM)	•Intrastriatal administration reduces striatal aspartate efflux (Miele et al., 2000)
			•Intra-VTA administration decreases striatal Glu and aspartate efflux (Miele et al., 2000)

(continued on next page)

Table 2 (*continued*)

System	Species	Dose/dosage[a]	Representative neurobiological effects of amphetamine
Opioids			
	Rat	0.5–5.5 mg/kg	•Increases NAcc endorphin efflux (Olive et al., 2001) •Reduces neuronal inhibition in the NAcc induced by κ-opioid receptor agonists (U69593 and dynorphin) (Xia et al., 2008) •Increases striatal PPE and PPD mRNA expression (Wang and McGinty, 1996; McGinty et al., 2011) •Increases in striatal mRNA PPE and PPD expression blocked by D_1 receptor antagonist SCH 23390; increases in PPD mRNA expression blocked by the D_2 receptor antagonist eticlopride (Wang and McGinty, 1996) •μ-/κ-opioid antagonists (naltrexone) attenuate reinstatement of amphetamine self-administration (Haggkvist et al., 2009a,b) •Repeated exposure (4 d) decreases whole brain endorphin content (Zhou et al., 2010) •Repeated exposure (5 d) increases cFOS expression in striatum and nucleus accumbens enkephalin-positive neurons (Mattson et al., 2007)
		30 μm–1 mM (incubation)	•δ-opioid agonist (SC80) enhances amphetamine-stimulated striatal synaptosome DA release (Bosse et al., 2008)
	Human	0.5 mg/kg or 30 mg	•Opioid antagonist (naltrexone) reduces the subjective "high" associated with amphetamine (Jayaram-Lindstrom et al., 2004, 2008) •Amphetamine reduces binding of a μ-opioid agonist (carfentanil) in striatum and frontal cortex, as measured by PET (Colasanti et al., 2012)
Cannabinoids			
	Mouse	2.0–2.5 mg/kg	•Amphetamine-stimulated motor activity absent in CB_1-deficient mice (Tzavara et al., 2009) •CB_1 antagonist (SR141716A) attenuates amphetamine-stimulated motor activity (Tzavara et al., 2009) •Nonspecific cannabinoid antagonist (WIN 55 212-2) and a CB_1 receptor antagonist (rimonabant) attenuate anxiogenic effects of acute amphetamine and anxiolytic effects of repeated amphetamine (9 d) (Biala et al., 2009)
	Rat	0.5–2.0 mg/kg	•CB_1 antagonist (SR141716A) attenuates amphetamine-stimulated DA efflux in NAcc (Kleijn et al., 2012) •Cannabidiol enhances neuronal oxidative stress in cortex, hippocampus, and striatum produced by 14 d of amphetamine and attenuates neuronal oxidative stress in hippocampus after 7 d of amphetamine exposure (Valvassori et al., 2011)
		2–10 μm (incubation)	•CB_1 antagonist (AM251) attenuates amphetamine-induced suppression of neuronal activity in lateral amygdala (Huang et al., 2003) •CB_1 antagonist (AM251) attenuates amphetamine-induced LTD in lateral amygdala (Huang et al., 2003)
ACh			
	Rat	1–2 mg/kg (systemic)	•Increases basal forebrain, frontal cortical, hippocampal, and striatal ACh efflux (Day and Fibiger, 1992; Imperato et al., 1993; Day and Fibiger, 1994; Acquas et al., 1997; Arnold et al., 2001) •Systemic D_1 (SCH23390) and D_2 (sulpiride) antagonists attenuate amphetamine-stimulated frontal cortical and hippocampal ACh efflux (Day and Fibiger, 1992, 1994) •Repeated exposure (4 d) decreases whole brain ACh content (Zhou et al., 2010)
		Intracranial infusion (50 μM)	•D_1 (SCH23390) and D_2 (sulpiride) antagonists block amphetamine-stimulated ACh efflux in the NAcc (Day and Fibiger, 1992, 1994)
BDNF			
	Mouse	5 mg/kg	•Partial depletion of BDNF prolongs amphetamine-stimulated motor activity (Saylor and McGinty, 2008) •Amphetamine-induced gene expression of striatal and cortical TrkB and BDNF and tyrosine hydroxylase in the SN*pc* is attenuated in mice partially deficient in BDNF levels (Saylor and McGinty, 2008)
	Rat	0.3–2.5 mg/kg	•Increases TrkB phosphorylation at the p-Tyr and the PLCγ phosphorylation sites of TrkB (816) in the NAcc and striatum (McGinty et al., 2011) •Increases TrkB expression in subregions of hippocampus (Shen et al., 2006) •Intrastriatal administration of a tyrosine kinase inhibitor (K525a) enhances amphetamine-stimulated motor activity and the induction of preprodynorphin mRNA expression (McGinty et al., 2011) •Repeated exposure (5 d) increases BDNF mRNA expression and immunoreactivity in basolateral amygdala and hypothalamus (Meredith et al., 2002) •Acute and repeated (5 d) exposure increases BDNF mRNA expression in piriform cortex (Meredith et al., 2002) •Repeated exposure (8 d) reduces BDNF levels in occipital cortex and hypothalamus (Angelucci et al., 2007)

3MT = 3-methoxytyramine; 5-HT_{1A} = serotonin receptor type 1A; 5-HT_2 = serotonin receptor type 2; 5-HT = serotonin; 5-HT-T = serotonin transporter; α_1 = adrenergic receptor type 1; α_2 = adrenergic receptor type 2; ACh = acetylcholine; AMPA = α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; BDNF = brain-derived neurotrophic factor; CB_1 = cannabinoid receptor subtype 1; CREB = cAMP response element binding protein; D_1 = dopamine receptor type 1; D_2 = dopamine receptor type 2; DA = dopamine; DAT = dopamine transporter; DHPG = dihydroxyphenylglycine; DOPAC = 3,4-dihydroxyphenylacetic acid; Glu = glutamate; GluA2 = subunit of the glutamate AMPA receptor; $GluN_2B$ = NMDA receptor subunit 2B; IBZM = iodobenzamide; K_i = inhibitory binding constant; LTD = long-term depression; LTP = long-term potentiation; mGluR5 = metabotropic glutamate receptor type 5; mGluR8 = metabotropic glutamate receptor type 8; MPEP = 2-methyl-6-(phenylethynyl)pyridine; MAO = monoamine oxidase; NAcc = nucleus accumbens; NE = norepinephrine; NET = norepinephrine transporter; NMDA = N-methyl-D-aspartate; PHCCC = n-phenyl-7-(hydroxy imino) cyclopropa [b]chromen-1a-carboxamide; PET = positron emission tomography; PPD = preprodynorphin; PPE = preproenkephalin; SN*pc* = substantia nigra *pars compacta*; TrkB = tyrosine kinase B receptor; VTA = ventral tegmental area.

[a] Systemic refers to intraperitoneal, intravenous, or subcutaneous administration.

In rats, systemic administration of the CB_1 antagonist SR141716A inhibits amphetamine-induced DA efflux in the ventral striatum but does not alter amphetamine-induced efflux of NE or 5-HT (Kleijn et al., 2012). Locomotor responses to amphetamine are also attenuated in mice after administration of SR141716A and in mice lacking the CB_1 receptor; these effects were reversed by coadministration of the mGluR5 antagonist MPEP but not the NMDA receptor antagonist MK-801 (Tzavara et al., 2009), suggesting that hyporesponsiveness to amphetamine in this model is associated with facilitation of Glu neurotransmission at the mGlu5 receptor but not at the NMDA receptor. In mice, the nonselective CB_1/CB_2 receptor agonist WIN 55,212-2 or the CB_1 inverse agonist rimonabant attenuate the anxiogenic effects of acute and subchronic amphetamine (Biala et al., 2009). As administration of WIN-55,212-2 alone produces anxiogenic effects in mice (Rutkowska et al., 2006), it is not known why both an agonist (WIN 55,212-2) and an inverse agonist (rimonabant) would reduce amphetamine-induced anxiety. However, it may be a context-dependent effect that is partially related to the enhanced DA activity associated with amphetamine administration.

8. Cholinergic system interactions

Acetylcholine (ACh) serves primarily a modulatory role in the CNS, with its effects being mediated by two receptor classes – nicotinic and muscarinic, of which there are multiple subtypes – that are present on presynaptic and postsynaptic neurons (Picciotto et al., 2012). Within the CNS, ACh plays a major role in learning and memory by influencing synaptic processes that promote neuronal burst firing and/or suppressing tonic neuronal activity (Picciotto et al., 2012).

Systemic administration of amphetamine increases ACh efflux in the basal forebrain, frontal cortex, and striatum in rats (Day & Fibiger, 1992; Imperato et al., 1993; Day & Fibiger, 1994; Acquas et al., 1997; Arnold et al., 2001). Stimulation of ACh efflux in the hippocampus, cortex, and caudate of rats by systemic amphetamine is attenuated by systemic administration of the D_1 receptor antagonist SCH23390 (Day & Fibiger, 1992; Imperato et al., 1993; Day & Fibiger, 1994), and stimulation of cortical ACh efflux by systemic amphetamine is attenuated by systemic administration of the D_2 receptor antagonist raclopride (Day & Fibiger, 1992, 1994). As the amphetamine-stimulated increase in striatal ACh efflux is not blocked by intrastriatal infusion of the D_1 antagonist SCH39166 (Acquas et al., 1997), it appears that the D_1 receptors that regulate ACh efflux following systemically administered amphetamine are located in extrastriatal regions. However, increases in nucleus accumbens ACh efflux in rats after administration of 50 μM amphetamine directly into the nucleus accumbens are blocked by coadministration of the D_1 antagonist SCH23390 (Keys & Mark, 1998). In this same study, the D_2 antagonist sulpiride did not alter the increases in nucleus accumbens ACh efflux associated with administration of 50 μM amphetamine, but it blocked the slight decrease in nucleus accumbens ACh efflux observed immediately after administration of 1 mM amphetamine (Keys & Mark, 1998).

9. Influences on synaptic plasticity

At its core, synaptic plasticity embodies adaptive mechanisms based on strengthening, as in long-term potentiation (LTP), and weakening, as in long-term depression (LTD), of synapses (Malenka & Bear, 2004); as part of this process, structural changes may also occur as neurons lose or form new synapses. Both LTP and LTD are implicated in a host of biological functions that are thought to form the basis of learning and memory (Geinisman, 2000; Geinisman et al., 2000), psychostimulant-induced behavioral locomotor sensitization (Horger et al., 1999), addiction and drug-seeking behavior (Grimm et al., 2003; Lu et al., 2004; Malenka & Bear, 2004), and fear conditioning (Mahan & Ressler, 2012). Amphetamine, through its diverse neurochemical effects, can potentially influence the intracellular and nuclear events that are required for synaptic plasticity to occur, and these effects may be relevant for processes related to learning and memory as well as addiction and fear conditioning (Wolf et al., 2004; Fukushiro et al., 2012; Mahan & Ressler, 2012; Gramage et al., 2013).

The enhancement of LTP associated with amphetamine administration is prevented by the D_1 receptor antagonist SCH23390, the β-adrenergic receptor antagonist propranolol, and by inhibition of cyclic adenosine monophosphate phosphokinase A (cAMP-PKA) signaling cascade, suggesting that amphetamine-associated enhancements of cortical LTP have a DA/NE-cAMP-PKA-sensitive component (Xu et al., 2010). Glu receptors, which also play a key role in synaptic plasticity (Henley & Wilkinson, 2013), may also mediate synaptic plasticity associated with amphetamine exposure. For example, LTP in VTA DA neurons in rats expressing an amphetamine-induced conditioned place preference is mediated by an upregulation of mGluR-dependent facilitation of burst-evoked calcium signaling (Ahn et al., 2010). Furthermore, chronic amphetamine administration downregulates the $GluN_2B$ subunit of the NMDA receptor on the synaptic surface membrane of rat striatal neurons, an alteration associated with a reduction in LTD (Mao et al., 2009). The plasticity associated with altered Glu systems is partially dependent on DA receptor activity, with D_2 receptor activation decreasing and D_1 receptor activation increasing GluR1 subunit expression in AMPA receptors in rat prefrontal cortex (Sun et al., 2005).

Amphetamine also has an effect on the formation of new synapses in the medial prefrontal cortex (Morshedi et al., 2009), which is an important step in mediating cognitive processes. For instance, the development of amphetamine-induced conditioned place preference (which is a form of associative or conditioned learning that is important in fear conditioning and addiction) is associated with increases in the number of excitatory synapses in the basolateral amygdala, an effect that is context dependent and is not observed with just repeated amphetamine exposure (Rademacher et al., 2010; Hetzel et al., 2012). The changes in synaptic plasticity and organization observed following repeated amphetamine exposure are likely to be mediated by multiple mechanisms, including increased synthesis of growth factors such as BDNF (Flores & Stewart, 2000).

Amphetamine, in addition to directly effecting synaptic plasticity and organization, influences BDNF, which is a trophic factor that is synthesized, stored, and released from neurons in an activity-dependent manner (Lu, 2003). The activation and consequent phosphorylation of the receptor for BDNF, TrkB, initiates intracellular signaling cascades that have multiple effects on synaptic plasticity (McAllister et al., 1999), Glu release (Lessmann, 1998), and NMDA receptor phosphorylation (Suen et al., 1997). The effects of amphetamine on BDNF signaling are complex and likely to be mediated by factors that include the level of exposure (both dose and duration). For example, in a study that determined BDNF mRNA levels in the rat brain 24 h after a single systemic dose of amphetamine (5 mg/kg) or after repeated amphetamine administration (5 mg/kg for 5 days), a single dose of amphetamine increased BDNF mRNA expression in the piriform cortex while repeated amphetamine administration increased BDNF mRNA expression and immunoreactivity in the basolateral amygdala, rostral piriform cortex, and paraventricular nucleus of the hypothalamus (Meredith et al., 2002) suggesting broader effects of amphetamine on BDNF expression. Enhanced TrkB expression in subregions of the hippocampus is also observed in the context of amphetamine-conditioned place preference (Shen et al., 2006). Consistent with this observation, acute administration of amphetamine increased TrkB phosphorylation at the p-Tyr and the PLCγ phosphorylation sites of TrkB in the nucleus accumbens and striatum (McGinty et al., 2011). As phosphorylation of TrkB occurs following activation of the receptor by BDNF, these data indirectly support the idea that amphetamine increased BDNF availability, although the mechanism(s) by which neurons may release BDNF in response to amphetamine administration is unclear. With more prolonged exposure (9 days), lower doses of amphetamine (1.5 mg/kg/day) reduce BDNF levels in the hypothalamus and occipital cortex (Angelucci et al., 2007). The discrepancy between these studies could reflect differences between changes in transcription versus changes in protein expression of BDNF, or it may represent the effect of chronic versus acute treatment.

10. Clinical implications for the use of amphetamine in neuropsychiatric disorders

Given the diverse neurobiological effects of amphetamine on monoamines, ACh, Glu, opioids, cannabinoids, synaptic plasticity, and neurotrophic factors and the influences on these systems on an array of neurobehavioral processes, including cognitive function (McAllister et al., 1999; Wolf et al., 2004; Picciotto et al., 2012), it is perhaps not surprising that amphetamine may have possible clinical utility for various neuropsychiatric disorders. Highlighted below is a broad overview of how increased knowledge of amphetamine's broad preclinical pharmacology may be relevant in selected neuropsychiatric disorders.

10.1. Attention-deficit/hyperactivity disorder

Amphetamine-based stimulants are first-line treatment options for ADHD (Seixas et al., 2011), with evidence that they demonstrate short-term efficacy versus placebo and long-term effectiveness for the core symptoms of ADHD (Hodgkins et al., 2012; Adler et al., 2013). A systematic review of 13 US and ex-US guidelines on ADHD noted that all guidelines recommend the use of amphetamine-based stimulants

as treatment options in individuals with ADHD (Seixas et al., 2011). Furthermore, a meta-analysis of 32 published articles investigating the efficacy of stimulant versus nonstimulant options for treating ADHD indicated that stimulants exhibited significantly greater treatment effect sizes than did nonstimulants (Faraone, 2009).

Cognitive dysfunction, including executive dysfunction, is also a core deficit of ADHD (Boonstra et al., 2005; Brown, 2008). Several recently published reviews suggest that there is evidence that psychostimulants, such as methylphenidate and amphetamine, can improve some aspects of cognition in individuals with ADHD. One literature review concluded that stimulant treatment is associated with improvements in a wide range of cognitive functions (Swanson et al., 2011). However, the data have been relatively inconsistent and the effective doses can vary greatly (Bidwell et al., 2011; Swanson et al., 2011).

The most frequently reported adverse events associated with amphetamine treatment in individuals with ADHD include insomnia, decreased appetite, weight loss, headache, stomach upset, and increased heart rate and blood pressure (Santosh et al., 2011; Duong et al., 2012; Vaughan & Kratochvil, 2012). Two safety concerns related to the use of stimulants in ADHD include the potential for adverse cardiovascular outcomes (Westover & Halm, 2012) and for abuse liability/nonmedical use (Hodgkins et al., 2012), as amphetamines are schedule II controlled substances (Panagiotou et al., 2011). The neurotransmitter systems responsible for stimulant-associated adverse events and safety concerns are in large part related to stimulation of peripheral NE activity (i.e., blood pressure and cardiovascular effects (Duong et al., 2012; Westover & Halm, 2012)) and central DA and NE activity (i.e., abuse liability) (Koob, 2006). Overall, stimulants have been used for more than 50 years for treatment of ADHD in multiple populations (i.e., children, adolescents and adults) allowing the clinical community to experience both the short- and long-term impact of this treatment option.

10.2. Narcolepsy

The hyperarousal psychostimulant effects of amphetamine are well documented and are most likely related to increased striatal and cortical DA availability (Wisor et al., 2001). Other neurotransmitter systems that are modulated by amphetamine, including ACh and NE, are also associated with increased arousal and vigilance (Datta & Maclean, 2007; Lee & Dan, 2012). Narcolepsy, which is primarily a disorder of orexin/histamine systems (Taheri et al., 2002), affects many forebrain monoamine pathways, leading to sudden and rapid transitions from wake to REM sleep during daytime and is often accompanied by cataplexy (loss of motor control) (John et al., 2004; Morgenthaler et al., 2007). Along with modafanil and armodafanil, methylphenidate is a first-line treatment option for daytime sleepiness due to narcolepsy (Morgenthaler et al., 2007). With modafinil and armodafinil being less stringent schedule IV controlled substances, (Hirai & Nishino, 2011), the clinical community tends to use these agents more frequently than stimulants as first line therapy for narcolepsy. The adverse event profile for amphetamine reported in individuals with narcolepsy includes irritability, mood changes, headache, palpitations, and insomnia (Hirai & Nishino, 2011).

10.3. Major depressive disorder

Forebrain monoamine (5-HT, DA, and NE) hypofunction remains the primary hypothesis to explain the symptoms of MDD, with the primary mood dysfunction most likely affected by 5-HT and NE (Ruhe et al., 2007). Other core symptoms of MDD, including anhedonia, anergia, fatigue, psychomotor retardation, and loss of motivation, are more influenced by DA (Berridge, 2007; Buyukdura et al., 2011). Cognitive dysfunction, which is also a core symptom of MDD (McDermott & Ebmeier, 2009; Marazziti et al., 2010), is likely influenced by both NE and DA systems (Arnsten & Li, 2005). The discussion about these systems in MDD comes from preclinical evidence (Savitz et al., 2009; Pradhan et al., 2011; Mathews et al., 2012). However, multiple studies did not report significant improvements in depressive symptoms following augmentation with methylphenidate (Postolache et al., 1999; Patkar et al., 2006; Ravindran et al., 2008) or the wake-promoting agent modafinil (DeBattista et al., 2003; Fava et al., 2005; Dunlop et al., 2007), possibly due to the study populations included in those studies.

In further regard to MDD, it is also important to note that newer hypotheses are being developed that point to roles for neurotrophic support, neurogenesis, and neuronal plasticity in MDD (Autry & Monteggia, 2012; Eisch & Petrik, 2012; Jun et al., 2012), as well as a role for Glu (Sanacora et al., 2012). It is pertinent therefore that amphetamine not only enhances DA and NE availability in brain regions of relevance to MDD, but also increases neurotrophin activity (Meredith et al., 2002; Shen et al., 2006; McGinty et al., 2011) and synaptic plasticity (Wolf et al., 2004), presumably by its actions on the Glu system. Amphetamine's ability to modulate the endogenous opiates may also contribute to its utility in MDD, as a study highlighted the potential role of the endogenous opiate system in MDD (Kennedy et al., 2006).

10.4. Schizophrenia

The “dopamine hypothesis of schizophrenia”, which encompasses hyperactive mesolimbic and hypoactive mesocortical DA pathways, is one of the enduring hypotheses to explain the positive and negative/cognitive symptoms of schizophrenia (Howes & Kapur, 2009). Data indicating that amphetamine causes a greater release of striatal DA in schizophrenic patients compared with normal controls (Laruelle et al., 1996) provides additional supportive evidence for the hyperdopaminergic hypothesis of schizophrenia. The role of cortical DA is less clear in the etiology of negative (and cognitive) symptoms, which remain unmet medical needs in the treatment of schizophrenia (Nuechterlein et al., 2004; Kirkpatrick et al., 2006). A role for NMDA receptor hypofunction in the pathophysiology of schizophrenia has also been proposed (Gonzalez-Burgos & Lewis, 2012).

There are currently no active clinical programs for amphetamine-based stimulants in the treatment of schizophrenia. However, there is a history of research on the adjuctive use of amphetamine in schizophrenia in individuals being treated with antipsychotics. Psychostimulants, when given as monotherapy, can exacerbate the positive symptoms of schizophrenia in actively ill, unstable, and unmedicated patients (Janowsky & Davis, 1976; Angrist et al., 1985; Jody et al., 1990; Levy et al., 1993). For example, in a study by Angrist et al. (1985), individuals stable for less than 30 days exhibited significantly greater increases in psychotic symptoms in response to amphetamine than did those who were stable for 30 days or longer. When used adjunctively or at lower doses in individuals being treated with an antipsychotic, the risk for psychostimulant-induced increases in psychotic symptoms was reduced (van Kammen & Boronow, 1988; Jody et al., 1990). This suggests that the D_2 receptor blockade induced by an antipsychotic can partially mitigate the impact of psychostimulant-induced increases in DA. Improvements in negative symptoms may be partially the result of the ability of amphetamine-stimulated cortical DA release to activate cortical D_1 receptors (which are not blocked by antipsychotics) and subsequently enhance ACh availability (Day & Fibiger, 1992, 1994) and NMDA receptor signaling (Jay, 2003; Lisman et al., 2011). In further support for the adjunctive use of psychostimulants in schizophrenia, a comprehensive literature review recently concluded that the adjunctive use of psychostimulant compounds can improve negative symptoms in carefully selected patients, in part due to their ability to stimulate mesocortical pathways (Lindenmayer et al., 2013). One recently published preliminary open-label clinical trial specifically assessed the effects of adjunctive lisdexamfetamine to a stable dose of atypical antipsychotic therapy in adults with clinically stable schizophrenia and predominant negative symptoms (Lasser

et al., 2013). However, large, placebo-controlled randomized clinical trials are required to address the safety and efficacy of adjunctive psychostimulants for treating a subset of schizophrenia symptoms.

10.5. Bipolar disorder

Compared with MDD and schizophrenia, less is understood regarding the neurobiology of bipolar disorder. Changes in all three monoamine systems (Walderhaug et al., 2011), along with altered Glu function (Sanacora et al., 2012), have been reported in bipolar disorder, which is characterized by transitions between hypomania, mania, and depressive states; however, it has been reported that cognitive function is also impaired in bipolar disorder (Gildengers et al., 2012). Two small studies reported clinical improvement following adjunctive treatment with amphetamine in individuals with bipolar I or II disorder experiencing residual depressive symptoms and medication-induced sedation (Carlson et al., 2004) and in individuals experiencing an acute manic episode (Garvey et al., 1987). Furthermore, adjunctive lisdexamfetamine dimesylate improved depressive symptoms and exhibited a beneficial effect on body weight and metabolic parameters in individuals with bipolar I/II disorder and comorbid ADHD in a small open-label study (McIntyre et al., 2013). However, there are no large randomized, controlled trials of adjunctive stimulant medications in bipolar disorder, which would be needed to draw definitive conclusions. Additionally, similar to the concerns regarding worsening psychotic symptoms in individuals with schizophrenia treated with stimulants, there are concerns regarding increasing manic symptoms in individuals with bipolar disorder treated with psychostimulants without concomitant antipsychotic medication.

11. Discussion and summary

Amphetamine has historically been considered a DA- and NE-enhancing agent, with a mechanism of action involving reversal of catecholamine reuptake via inhibition of monamine reuptake transporters, vesicular reuptake transporters, and MAO. Although it is true that amphetamine enhances the synaptic availability of DA and NE in several brain regions, there is now substantial evidence from preclinical studies that amphetamine has a broader range of neurobiologic effects. In the current review, evidence for the involvement of 5-HT, ACh, Glu, endogenous opioids, endocannabinoids, and BDNF signaling in the neurobiologic effects of amphetamine is summarized. Furthermore, evidence in support of an influence of amphetamine on synaptic plasticity – most likely as a consequence of its diverse neurochemical effects – is provided. These wide-ranging effects may underpin not only the abuse liability of amphetamine but may also be therapeutically relevant in neuropsychiatric disorders that are characterized by pathophysiologies that include maladaptive neuronal processes.

Although approved for use as monotherapy in the treatment of ADHD and narcolepsy, there may be an exacerbation of some symptoms in other neuropsychiatric disorders when amphetamine is administered alone. However, emerging data on the interactions of amphetamine with diverse neurotransmitter systems suggest amphetamine-based stimulants may have a broader role in alleviating some symptoms associated with neuropsychiatric disorders than previously considered when used as adjunctive therapy. Taken together, the data described in this review should help to remind the reader of the broad array of neurobiologic effects associated with amphetamine and encourage further research on the preclinical pharmacology of amphetamine and its implications for the treatment of neuropsychiatric disorders.

Conflict of interest

P. Hutson and M. Madhoo are employees of Shire Development LLC and hold stock and/or stock options in Shire.

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A. Patkar is a consultant for Avanir Pharma, Gilead, and Dey Pharma; is on the speakers bureau for and received honoraria from Alkermes, Bristol-Myers Squibb, Dey Pharma, Merck, Sunovion and Pfizer; and has received grant support from the National Institutes of Health (NIDA, NIAAA), SAMHSA, AstraZeneca, Bristol-Myers Squibb, Cephalon, Forest, Johnson & Johnson, Jazz Pharmaceuticals, Lundbeck, Merck, Organon, Pfizer, Sunovion, Shire, and Titan. He is not a major stockholder in or employee of and has not received other material support from pharmaceutical companies.

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