ACTIONS OF 3,4-METHYLENEDIOXYMETHAMPHETAMINE (MDMA) ON CEREBRAL DOPAMINERIC, SEROTONERGIC AND CHOLINERGIC NEURONS

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Abstract

3,4-Methylenedioxymethamphetamine (MDMA) is an amphetamine derivative and a popular drug of abuse that exhibits mild hallucinogenic and rewarding properties and engenders feelings of connectedness and openness. The unique psychopharmacological profile of this drug of abuse most likely is derived from the property of MDMA to promote the release of dopamine and serotonin (5-HT) in multiple brain regions. The present review highlights primarily data from studies employing in vivo microdialysis that detail the actions of MDMA on the release of these neurotransmitters. Data from in vivo microdialysis experiments indicate that MDMA, like most amphetamine derivatives, increases the release of dopamine in the striatum, n. accumbens and prefrontal cortex. However, the release of dopamine evoked by MDMA in each of these brain regions appears to be modulated by concomitantly released 5-HT and the subsequent activation of 5-HT2A/C or 5-HT2B/C receptors. In addition to its stimulatory effect on the release of monoamines, MDMA also enhances the release of acetylcholine in the striatum, hippocampus and prefrontal cortex, and this cholinergic response appears to be secondary to the activation of histaminergic, dopaminergic and/or serotonergic receptors. Beyond the acute stimulatory effect of MDMA on neurotransmitter release, MDMA also increases the extracellular concentration of energy substrates, e.g., glucose and lactate in the brain. In contrast to the acute stimulatory actions of MDMA on the release of monoamines and acetylcholine, the repeated administration of high doses of MDMA is thought to result in a selective neurotoxicity to 5-HT axon terminals in the rat. Additional studies are reviewed that focus on the alterations in neurotransmitter responses to pharmacological and physiological stimuli that accompany MDMA-induced 5-HT neurotoxicity.

1. Introduction

3,4-Methylenedioxymethamphetamine (MDMA, Ecstasy) is a phenylethylamine that was first synthesized by Merck in 1912, although it was not pursued at that time as a potential therapeutic agent (Freudenmann et al., 2006). As a synthetic amphetamine derivative, MDMA exhibits both psychostimulant and mild hallucinogenic properties (Shulgin, 1986). MDMA also is often described as an entactogen which means to produce a sense of touching within. The subjective effects of MDMA in humans include a sense of well being, connectedness, diminished

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aggression, increased sensitivity to color and altered perception of time (McDowell and Kleber, 1994; Davison and Parrott, 1997). The ability of MDMA to enhance feelings of openness and trust in its users (Grinspoon and Bakalar, 1986) was the basis for the use of the drug as adjunct to psychotherapy during the 1980s.

It has been well established that amphetamine derivatives enhance the release of monoamine neurotransmitters. The unique pharmacological profile of MDMA in humans may result from the simultaneous release of 5-HT and dopamine (DA), and perhaps acetylcholine (ACh), in multiple brain regions. Consistent with the view that serotonergic and dopaminergic mechanisms are generally considered to underlie the hallucinogenic and psychomotor stimulant properties of phenylethylamines, Liechti et al (2000) have reported that many of the subjective effects of MDMA in human volunteers are antagonized by the administration of a 5-HT2 antagonist. In consideration of these neurochemical substrates underlying the actions of MDMA, herein we review studies, including those that have employed the technique of in vivo microdialysis, that focus on the acute effects of MDMA on extracellular concentrations of DA and 5-HT, as well as ACh, and the various receptors and transporters that contribute to these effects. Finally, the impact of exposure to neurotoxic regimens of MDMA on the subsequent release of DA, 5-HT and ACh evoked by pharmacological and physiological stimuli also is reviewed.

2. Acute stimulatory effects of MDMA

2.1. Dopaminergic neurons

2.1.1. Striatum—Under in vitro conditions MDMA has been shown to promote the release of DA from superfused brain slices, as well as prevent the reuptake of DA into brain synaptosomes (Johnson et al., 1986; Schmidt et al., 1987; Johnson et al., 1991; Steele et al., 1987). Moreover, Crespi et al. (1997) demonstrated that the MDMA-induced release of DA from striatal synaptosomes is carrier-mediated and calcium dependent.

Yamamoto and Spanos (1988) using in vivo voltammetry were among the first to demonstrate that MDMA at behaviorally relevant doses (i.e., 5–10 mg/kg) increases the release of striatal DA in vivo. Numerous other investigators have confirmed these findings using in vivo microdialysis (Hiramatsu and Cho, 1990; Gough et al., 1991; Nash and Nichols, 1991; Sabol and Seiden, 1998; Estaban et al., 2001; Gudelsky et al., 1994). The release of DA elicited by MDMA within the striatum is thought to involve both transporter- and impulse-dependent processes. The MDMA-, as well as amphetamine-, induced increase in the extracellular concentration of DA in the striatum is attenuated by treatment with inhibitors of the DA transporter, e.g., nomifensine, mazindol, GBR12909 (Hurd and Ungerstedt, 1989; Westerink et al., 1987; Nash and Brodkin, 1991; Shankaran et al., 1999b). However, whereas amphetamine-induced DA release is unaffected by the sodium channel blocker tetrodotoxin (TTX), TTX diminishes MDMA-induced increase in striatal DA release (Yamamoto et al., 1995).

The impulse dependent process that contributes to the MDMA-induced release of DA within the striatum appears to involve a facilitatory effect of 5-HT acting on 5-HT2 receptors. First, whereas fluoxetine enhances amphetamine-induced DA release in the striatum, this 5-HT reuptake inhibitor suppresses DA release stimulated by MDMA (Gudelsky and Nash, 1996; Koch and Galloway, 1997; Shankaran et al., 1999a) (Figure 1). Thus, amphetamine- and MDMA-induced increases in striatal DA release are differentially affected by both TTX and fluoxetine. The differential effect of fluoxetine on the DA response to these two stimulants is likely due to the fact that fluoxetine provides a modest increase in extracellular 5-HT, thereby providing a state-dependent facilitation of the actions of amphetamine. In contrast, fluoxetine

prevents the MDMA-induced increase in 5-HT release (Gudelsky and Nash, 1996), thereby removing the stimulatory influence of 5-HT on MDMA-induced DA release.

The involvement of 5-HT2 receptors in the facilitatory effect of 5-HT on stimulated DA release is evidenced by the finding that 5-HT2 agonists potentiate (Gudelsky et al., 1994) and 5-HT2 antagonists suppress (Nash, 1990; Schmidt et al., 1994; Yamamoto et al., 1995) the MDMA-induced increase in striatal DA release. Yamamoto et al (1995) also demonstrated that blockade of 5-HT2A/2C receptors in either the striatum or the substantia nigra results in a blunting of the MDMA-induced release of striatal dopamine. Yamamoto et al (1995) further demonstrated that MDMA, but not amphetamine, produces a 5-HT2 receptor dependent decrease in GABA release in the substantia nigra. Thus, activation of 5-HT2 receptors in the striatum and substantia nigra may contribute to a disinhibition of striatal DA release through attenuation of GABA-mediated feedback control in the substantia nigra.

Inasmuch as 5-HT2 receptors modulate MDMA-induced DA release in the striatum, and these receptors are known to utilize protein kinase C (PKC) for intracellular signaling (Conn and Sanders-Bush, 1986), Nair and Gudelsky (2004a) examined the effects of modulation of PKC activity on MDMA-induced DA release. The MDMA-induced increase in extracellular concentrations of DA in the striatum was shown to be potentiated by activation of PKC and suppressed in animals treated with a PKC inhibitor. In contrast, inhibition of PKC did not alter amphetamine-induced DA release in the striatum (Figure 2). These results are consistent with the view that 5-HT release elicited by MDMA, but not amphetamine, and the subsequent activation of 5-HT2 receptors linked to PKC in the striatum functions to facilitate MDMA-induced DA release.

2.1.2. Nucleus Accumbens—MDMA also increases the release of DA in other brain regions containing the terminals of mesocorticolimbic neurons. Several investigators have demonstrated that MDMA produces a marked increase in the extracelllular concentration of DA in the n. accumbens (Cadoni et al., 2005; Kankaanpaa et al., 1998; Marona-Lweicka et al., 1996; Amato et al., 2007; O-Shea et al., 2005; Bankson and Yamamoto, 2004). As in the striatum, MDMA-induced DA release in the n. accumbens appears also to be modulated by 5-HT-GABA interactions. However, the nature of the modulatory influence of 5-HT-GABA on MDMA-induced DA release within the mesolimbic pathway is opposite in direction to that in the nigrostriatal system. As noted above, MDMA-induced suppression of nigral GABA release following 5-HT2A/2C receptor activation disinhibits striatal DA release. However, an MDMA-induced increase in GABA release within the ventral tegmental area (VTA), subsequent to 5-HT2B/C receptor activation, appears to limit the magnitude of MDMA-induced DA release in the n. accumbens (Bankson and Yamamoto, 2004).

Finally, O'Shea and coworkers have investigated the influence of ambient temperature on MDMA-induced DA and 5-HT release in the n. accumbens and striatum (O'Shea et al., 2005). These investigators demonstrated that the increase in the extracellular concentration of DA, as well as 5-HT, in the n. accumbens, but not striatum, is greater at 30° C than at 20°C. On the basis of these results, O'Shea et al (2005) have suggested that the rewarding properties of MDMA may be more pronounced at higher ambient temperatures (O'Shea et al., 2005).

2.1.3. Prefrontal Cortex—The systemic administration of MDMA has been shown to enhance the release of DA within the medial prefrontal cortex (PFC), and this response, like that in the striatum, also appears to be modulated by the activity of PKC that is presumably linked to the activation of 5-HT receptors in this brain region. However, in contrast to the finding that inhibition of striatal PKC blunts MDMA-induced DA release in the striatum (Nair and Gudelsky, 2004a), the MDMA-induced release of DA in the PFC is enhanced following inhibition of PKC in this brain region (Nair and Gudelsky, 2004a). These findings suggest that

PKC signaling through 5-HT2 receptors in the PFC may function to limit stimulated DA release in this brain region in contrast to its role to facilitate stimulated DA release in the striatum. Although this view is inconsistent with the conclusion of Pehek et al (2001) that 5-HT2A receptors within the PFC function to facilitate stimulated DA release in the PFC, other studies suggest that 5-HT2C receptors may function to limit stimulated DA release in this brain region (Bonaccorso et al., 2002). Regardless of the identity of the 5-HT receptor subtypes linked to PKC, it seems clear that the MDMA-induced release of DA in the striatum and PFC is differentially affected by inhibition of PKC activity.

2.1.4. Hippocampus—Although the hippocampus is only sparsely innervated by dopaminergic terminals (Scatton et al., 1981), the administration of MDMA also results in a striking increase in the extracellular concentration of DA in the ventral hippocampus (Shankaran and Gudelsky, 1998). Importantly, the MDMA-induced increase in hippocampal, but not striatal, DA release was shown by these investigators to be blunted in animals treated with desipramine, as well as in animals in which noradrenergic neurons were lesioned with DSP-4. On the basis of these results, Shankaran and Gudelsky (1998) suggested that noradrenergic nerve terminals are the source of the increase in extracellular DA in the hippocampus following MDMA administration.

An additional mechanism by which high doses of MDMA may increase extracellular concentrations of DA in the hippocampus is through an increase in brain tyrosine (Breier et al., 2006). However, the increase in DA produced by elevations in tyrosine does not appear to be through activation of tyrosine hydroxylase but rather through the non-enzymatic hydroxylation of tyrosine to DOPA caused by the increase in hydroxyl radicals following administration of MDMA (Shankaran et al., 1999a, b; Colado et al., 1997). The L-DOPA formed through this pathway can then be converted to DA via aromatic amino acid decarboxylase in 5-HT neurons. This aberrant formation of DA within presumably 5-HT neurons may not only contribute to MDMA-induced DA release in the DA-sparse hippocampus but also may contribute to DA-derived oxidative damage to 5-HT terminals (Breier et al., 2006).

2.2. Serotonergic neurons

MDMA has been shown to increase the release of 5-HT both in vitro and in vivo. Under in vitro conditions, the release of 5-HT is increased from brain slices, synaptosomes and cultured neurons following exposure to MDMA (Nichols et al., 1982; Johnson et al., 1986; Berger et al., 1997; Crespi et al., 1997; Azmitia et al., 1990; Sprouse et al., 1989). The MDMA-induced release of 5-HT in vitro is suppressed in the presence of drugs that inhibit the activity of the 5-HT transporter indicating that the increase in release of 5-HT likely occurs through the 5-HT transporter (Hekmatpanah and Peroutka, 1990; Gu and Azmitia, 1993; Koch and Galloway, 1993).

Data from microdialysis studies also indicate that MDMA enhances the release of 5-HT in vivo in numerous brain regions. The administration of MDMA has been reported to result in a dose-dependent increase in the extracellular concentration of 5-HT in the striatum, hippocampus and cortex (Gough et al., 1991; Gudelsky and Nash, 1996). Consistent with results from in vitro studies, inhibition of the 5-HT transporter with fluoxetine suppresses MDMA-induced 5-HT release in vivo (Gudelsky and Nash, 1996; Mechan et al., 2002), thereby further supporting the conclusion that MDMA facilitates the transporter-mediated release of 5-HT.

MDMA also has been reported to interfere with 5-HT metabolism (Leonardi and Azmitia, 1994). Thus, an action of MDMA to increase the intraneuronal accumulation of 5-HT may also contribute to the magnitude of 5-HT efflux evoked by MDMA.

The administration of 5-hydroxytryptophan (5-HTP) results in a modest increase in the extracellular concentration of 5-HT (Gartside et al., 1997), and the magnitude of the increase is enhanced by co-administration of a decarboxylase inhibitor or inhibitor of the 5-HT transporter (Perry and Fuller, 1993; Gudelsky and Nash, 1996). Although 5-HTP induced 5-HT release is thought to involve impulse-dependent processes (Gartside et al., 1997), the 5-HTP-induced increase in 5-HT synthesis also can facilitate 5-HT efflux through the 5-HT transporter. Gudelsky and Nash (1996) demonstrated that the co-administration of carbidopa/5-HTP and MDMA results in a dramatic increase in extracellular 5-HT that is 10 times greater than that produced by carbidopa/5-HTP alone. The contribution of newly synthesized 5-HT to the MDMA-stimulated release of 5-HT also was demonstrated by Brodkin et al (1993) who reported that inhibition of 5-HT synthesis markedly attenuates the MDMA-induced increase in extracellular 5-HT. Thus, the release of newly synthesized 5-HT that can be facilitated by treatment with precursors may be enhanced further by psychostimulants that activate the 5-HT transporter.

2.3. Cholinergic neurons

The effects of MDMA on the release of DA and 5-HT have been well documented, and it is likely that the MDMA-induced release of DA accounts for the mild euphoriant and rewarding properties of the drug, whereas the stimulated release of 5-HT may account for the other subjective effects of MDMA. However, the purported involvement of DA and 5-HT in the subjective effects of MDMA does not preclude the involvement of other neurotransmitter systems in the psychopharmacology of this drug of abuse.

Recent studies have examined the effects of MDMA on central cholinergic neurons. Fischer et al (2000) demonstrated that MDMA enhances the release of ACh in vitro from striatal slices. Furthermore, evidence was provided that this effect of MDMA involves a direct activation of H1 histamine receptors by MDMA.

Consistent with the results of Fischer et al (2000), Acquas et al (2001) employed in vivo microdialysis to demonstrate that MDMA increases the extracellular concentration of ACh in the PFC and striatum. In other recent studies, Nair and Gudelsky (2005, 2006a) have further characterized the stimulatory effect of MDMA in vivo on ACh release within the PFC and hippocampus. ACh release in these two brain regions was shown to be increased for a prolonged period (>5 hours) following the systemic administration of 3–20 mg/kg of MDMA (Figure 3). The local perfusion of MDMA within these brain regions also resulted in an increased extracellular concentration of ACh in the PFC and hippocampus. It was also noted by Nair and Gudelsky (2005), that (+)- an (−)-MDMA exhibit similar potencies in enhancing ACh release in the PFC. Interestingly, (+)- and (−)-MDMA exhibit similar potencies in the inhibition of uptake and stimulation of 5-HT release (Johnson et al., 1986; Steele et al., 1987), whereas the (+)-enantiomer of MDMA is more potent in releasing DA than the (−)-enantiomer (Steele et al., 1987; Hirmatsu et al., 1988).

The stimulatory effect of MDMA on ACh release in the PFC appears to involve both dopaminergic and serotonergic mechanisms, since this response is blunted in animals in which DA and 5-HT synthesis is inhibited (Nair and Gudelsky, 2006a). Although 5-HT2 receptor mechanisms appear to function to enhance ACh release in the PFC (Nair and Gudelsky, 2004), 5-HT2 receptor activation does not appear to contribute to the stimulatory effect of MDMA on ACh release in this brain region. Rather, the MDMA-induced increase in cortical ACh release has been shown to be blunted in animals treated with either a D1 antgonist or a 5-HT4 antagonist (Nair and Gudelsky, 2005). Thus, both D1 and 5-HT4 receptor subtypes contribute to the mechanism by which MDMA increases cortical ACh release. These results are consistent with previous work in which 5-HT4 agonists have been shown to increase ACh release in the PFC and 5-HT4 antagonists have been shown to attenuate the stimulatory effect of p-

choloramphetamine and indeloxazine, a 5-HT releasing agent, on cortical ACh release (Yamaguchi et al., 1997a, Yamaguchi et al., 1997b; Consolo et al., 1994). Moreover, activation of D1 receptors previously has been reported to increase ACh release in the PFC and antagonism of D1 receptors attenuates amphetamine-induced ACh release in the PFC (Damsma et al., 1990; Day and Fibiger, 1992; Imperato et al., 1993). To date, the localization of the D1 and 5-HT4 receptors mediating the stimulatory effect of MDMA on cortical ACh release is unknown.

Sarter and Bruno (1999) have proposed that hyperattentional impairments that accompany psychosis and hallucinations may be associated with increased cholinergic function in the cortex. In addition, increased cholinergic activity may contribute to an amplification of external stimuli. It is conceivable that the stimulatory effect of MDMA on cortical ACh release contributes to the mild hallucinations and increased sensitivity to sensory stimuli reported in human MDMA abusers.

Additionally, many psychostimulant drugs (e.g., amphetamine, cocaine, nicotine, methylphenidate) have been shown to increase ACh release in the cortex and hippocampus (Day and Fibiger, 1992; Imperato et al., 1993; Reid et al., 1993; Taguchi et al., 1998; Arnold et al., 2001). Inasumuch as cortical ACh may function in attentional processing (Sarter et al., 2003), it can be suggested that the stimulatory effect of these drugs of abuse on ACh release in the PFC contributes to the enhanced processing of drug associated environmental cues that accompany drug dependence.

2.4. Energy Substrates

In vivo microdialysis also has been employed to investigate the effects of MDMA on cerebral energy substrates (e.g., glucose, lactate) that may be altered as a result of the acute effects of MDMA on the aforementioned neurotransmitter systems. The systemic administration of MDMA results in a prolonged increase in the extracellular concentration of glucose in the striatum, hippocampus and prefrontal cortex (Darvesh et al., 2002; Pachmerhiwala et al., 2007; Gramsbergen and Cumming, 2007), as well as the extracellular concentration of lactate in the striatum (Gramsbergen and Cumming, 2007). The MDMA-induced increase in the extracellular concentration of energy substrates is prevented in rats in which 5-HT synthesis has been inhibited or in rats treated with a 5-HT reuptake inhibitor (e.g., fluoxetine) (Gramsbergen and Cumming, 2007; Pachmerhiwala et al., 2007). Pachmerhiwala et al (2007) also reported that adrenergic receptor antagonists prevent the increased glucose response to MDMA. Thus, both noradrenergic and serotonergic mechanisms appear to contribute to the actions of MDMA to increase cerebral glucose concentrations.

Although Darvesh et al (2002) originally suggested that the increase in brain extracellular glucose following MDMA may be a result of MDMA-induced glycogenolysis in brain, Gramsbergen and Cumming (2007) have speculated that increased brain glucose produced by MDMA is a result of increased peripheral blood glucose and increased glucose transport into brain, since these investigators have reported that MDMA produces a transient increase in peripheral blood glucose. However, other investigators have failed to confirm an effect of MDMA to increase blood glucose. Soto-Montenegro et al (2007) have reported that MDMA actually decreases peripheral glucose and Darvesh et al (2002) failed to find any significant effect of MDMA on blood glucose at a dose that elevated brain extracellular concentrations of glucose. Thus, the source of the increased extracellular glucose in brain following MDMA remains to be resolved, as well as its relationship to a potential increase in cerebral blood flow and/or tissue glucose utilization.

3. Long term effects of repeated MDMA administration

In addition to the acute effects of MDMA to enhance monoamine and ACh release, it is well documented that the repeated administration of MDMA results in a long-term reduction in brain tissue concentrations of 5-HT and reductions in 5-HT reuptake sites in rodents and non-human primates (c.f., Ricaurte et al., 2000; Green et al., 2003; Gudelsky and Yamamoto, 2003). On the basis of these neurochemical effects, MDMA is generally viewed to be selectively neurotoxic to 5-HT terminals. A full discussion of the mechanisms of MDMA-induced 5-HT neurotoxicity is beyond the scope of the present review. However, evidence supports roles for both oxidative and bioenergetic stress in the mechanisms underlying MDMA-induced 5-HT neurotoxicity (Gudelsky and Yamamoto, 2003; Darvesh and Gudelsky, 2005; Quinton and Yamamoto, 2006). Data from microdialysis studies that support the conclusion that MDMA induces oxidative stress include the findings that neurotoxic regimens of MDMA increase the formation of reactive oxygen species (e.g., hydroxyl radicals), as well as reactive nitrogen species (e.g., nitric oxide) (Colado et al., 1997; Shankaran et al., 1999a, Shankaran et al., 1999b; Darvesh et al., 2005). Furthermore, the acute activation of the DA and 5-HT transporters by MDMA or a toxic metabolite of MDMA appears necessary for MDMA-induced hydroxyl radical formation (Shankaran et al., 1999a, b; Camarero et al., 2003; Jones et al., 2005). Thus, activation of the DA and 5-HT transporters appears critical in linking the acute stimulatory effects of MDMA to the long-term neurotoxic effects of this drug of abuse.

Although alterations in markers of 5-HT axon terminals following the repeated administration of MDMA have been well characterized, the functional consequences of MDMA neurotoxicity are less well documented.

Acute treatment with MDMA results in a characteristic behavioral syndrome consisting of forepaw treading, head weaving and low body posture (Spanos and Yamamoto, 1989; Slikker et al., 1989). However, following a neurotoxic regimen of MDMA, the ability of a subsequent injection of MDMA to elicit the 5-HT behavioral syndrome has been shown to be greatly diminished (Shankaran and Gudelsky, 1999; Shankaran et al., 2001). Series et al (1995) and Baumann et al (1998) also have demonstrated that the acute behavioral effects of fenfluramine are diminished following treatment with 5-HT depleting regimens of p-choloramphetamine, fenfluramine or MDMA. Behavioral responses in monkeys to MDMA also have been reported to be diminished following a short course, high dose exposure to MDMA (Frederick et al., 1998). Inasmuch as the behavioral response to MDMA is considered to result from the drug-induced enhancement of the release of 5-HT, it has been concluded that 5-HT depleting regimens of MDMA result in a reduction in the ability of subsequent MDMA treatment to evoke 5-HT release. Indeed, Gartside et al (1996) reported that treatment of rats with a high dose regimen of MDMA results in a reduction in 5-HT release evoked by electrical stimulation of the raphe nucleus. It also has been demonstrated that the ability of MDMA to increase extracellular concentrations of 5-HT is significantly diminished in rats previously exposed to a neurotoxic regimen of MDMA (Shankaran et al., 2001; Amato et al., 2007). It was further demonstrated by Shankaran et al (2001) that concomitant treatment of rats with ascorbic acid with a neurotoxic regimen of MDMA not only prevents MDMA induced depletion of brain 5-HT but also the loss in ability of MDMA to evoke 5-HT release. This finding further supports the conclusion that MDMA-induced 5-HT neurotoxicity is accompanied by a reduction in the ability of pharmacological agents (e.g., MDMA) that are known 5-HT releasing agents to subsequently evoke 5-HT release in multiple brain regions.

The ability of a 5-HT depleting regimen of MDMA to alter neurotransmitter responses to physiological, rather than pharmacological, stimuli was further explored by Matuszewich et al (2002). It is well known that acute stressors increase extracellular DA and 5-HT in brain regions such as the PFC and hippocampus (Chaouloff et al., 1993; Abercrombie et al., 1989; Sorg and

Kalivas, 1993). Matuszewich et al (2002) demonstrated that the acute increases in extracellular 5-HT in the hippocampus and PFC elicited by immobilization stress were diminished in rats previously exposed to a neurotoxic regimen of MDMA. The neurotoxic regimen of MDMA also resulted in a diminished stress induced release of DA in the PFC. These data suggest that depletion of brain 5-HT following exposure to a neurotoxic regimen of MDMA compromises the ability of forebrain serotonergic, and in some cases dopaminergic, neurons to respond to stressful stimuli.

In view of the role of central cholinergic systems in attention, learning and cognitive processes, and evidence that rats and humans exposed repeatedly to MDMA exhibit psychological and cognitive abnormalities (Sprague et al., 2003; Wareing et al., 2000; Parrott et al., 2002; Renemann et al., 2001), Nair and Gudelsky (2006b) examined the effects of a 5-HT depleting regimen of MDMA on the subsequent stimulation of ACh release in the PFC. It was demonstrated that the increase in the extracellular concentration of ACh in the PFC elicited by MDMA was attenuated in rats previously exposed to a neurotoxic regimen of MDMA in much the same manner as has been reported for the MDMA induced increase in 5-HT release (Shankaran and Gudelsky, 1999; Shankaran et al., 2001). In contrast, physical (i.e., tail pinch) or psychological (i.e., intruder rat) stressors evoked a similar increase in ACh release in the PFC of control animals and animals previously exposed to a neurotoxic regimen of MDMA (Nair and Gudelsky, 2006b). Thus, it appears that although MDMA-induced depletion of brain 5-HT is accompanied by a suppression of subsequent MDMA-induced ACh release, cortical ACh release elicited by the stressors of pain or the novelty of an environmental intruder is not significantly affected by MDMA-induced 5-HT neurotoxicity.

The intermittent administration of amphetamine and methamphetamine, as well as cocaine, has repeatedly been demonstrated to result in behavioral and neurochemical sensitization that is characterized by augmented locomotor responses and augmented DA release in the n. accumbens in response to a stimulant challenge (c.f., Pierce and Kalivas, 1997). Several groups of investigators have demonstrated that the repeated administration of MDMA also results in long-term neuroadaptations in the mesolimbic DA pathway that are manifested as an enhancement of the locomotor stimulating effect of MDMA, i.e., behavioral sensitization (Kalivas et al., 1997; McCreary et al., 1999; Ramos et al., 2005). Kalivas et al (1997) also have shown that the repeated administration of MDMA results in cross-behavioral sensitization to the locomotor stimulating effect of cocaine. Eposure to a regimen of MDMA that produces 5-HT depletion also has been shown to result in neurochemical sensitization (Kalivas et al., 1997; Morgan et al., 1997). Thus, cocaine and MDMA-induced increases in the extracellular concentration of DA in the n. accumbens are enhanced in animals previously exposed to a 5-HT depleting regimen of MDMA. Amphetamine-induced behaviors also have been reported to be enhanced following depletion of brain 5-HT with p-chlorophenylalanine (Mabry and Campbell, 1973). Thus, it is unclear whether the behavioral and neurochemical sensitization that occurs following the administration of a neurotoxic regimen of MDMA involves the depletion of brain 5-HT or whether it involves mechanisms similar to those involved in sensitization elicited by the intermittent administration of low doses of psychomotor stimulants (c.f., Vanderschuren and Kalivas, 2000).

A long-term augmentation of mesolimbic DA activity also has been demonstrated following the exposure of rats to a neurotoxic regimen of MDMA together with chronic stress. Amato et al (2007) reported that rats treated with a neurotoxic regimen of MDMA followed by chronic unpredictable stress exhibit augmentation of the MDMA-induced increase in the extracellular concentration of 5-HT in the VTA and augmentation of DA responses in the n. accumbens. A role for 5-HT in the VTA in the sensitization of mesolimbic DA transmission was inferred from the finding that the local infusion of a 5-HT1B antagonist into the VTA blunted the

sensitization of DA release in the n. accumbens of animals exposed to repeated MDMA treatments and chronic unpredictable stress (Amato et al., 2007).

Inasmuch as stimulant induced sensitization often is considered a model for drug craving and dependence, the finding that repeated exposure to MDMA or MDMA together with stress results in sensitization of the mesolimbic DA pathway may have an implication for vulnerability to drug abuse in human abusers of this recreational drug. Alternatively, MDMA-induced neuroadaptations within the mesolimbic DA system may contribute to the psychological disturbances in some MDMA abusers.

4. Concluding Remarks

Although MDMA is an amphetamine derivative, the psychopharmacological profile of this drug is unique among phenylethylamine drugs of abuse, and its diverse pharmacology, in part, is summarized in figure 4. The neurochemical substrates that underlie MDMA's unique actions appear related to a combination of enhanced DA and 5-HT release in multiple brain regions. Furthermore, it can be envisioned that an enhancement of cortical and hippocampal ACh release also contributes to the subjective effects of MDMA.

The repeated exposure to MDMA results in a long term depletion of brain 5-HT in rodents, non-human primates, and presumably humans, that is the result of increased oxidative stress (e.g, free radical formation). Although the extent to which depletion of brain 5-HT by MDMA results in alterations in neurotransmitter responses to pharmacological and physiological stimuli is largely unknown, several studies have demonstrated alterations in neurotransmitter responses to pharmacological agents and stressors that accompany MDMA-induced 5-HT neurotoxicity. The extent to which long-term alterations in neurotransmitter responses associated with MDMA-induced 5-HT neurotoxicity contributes to cognitive and psychological disturbances sometimes seen in human abusers of MDMA remains to be determined.

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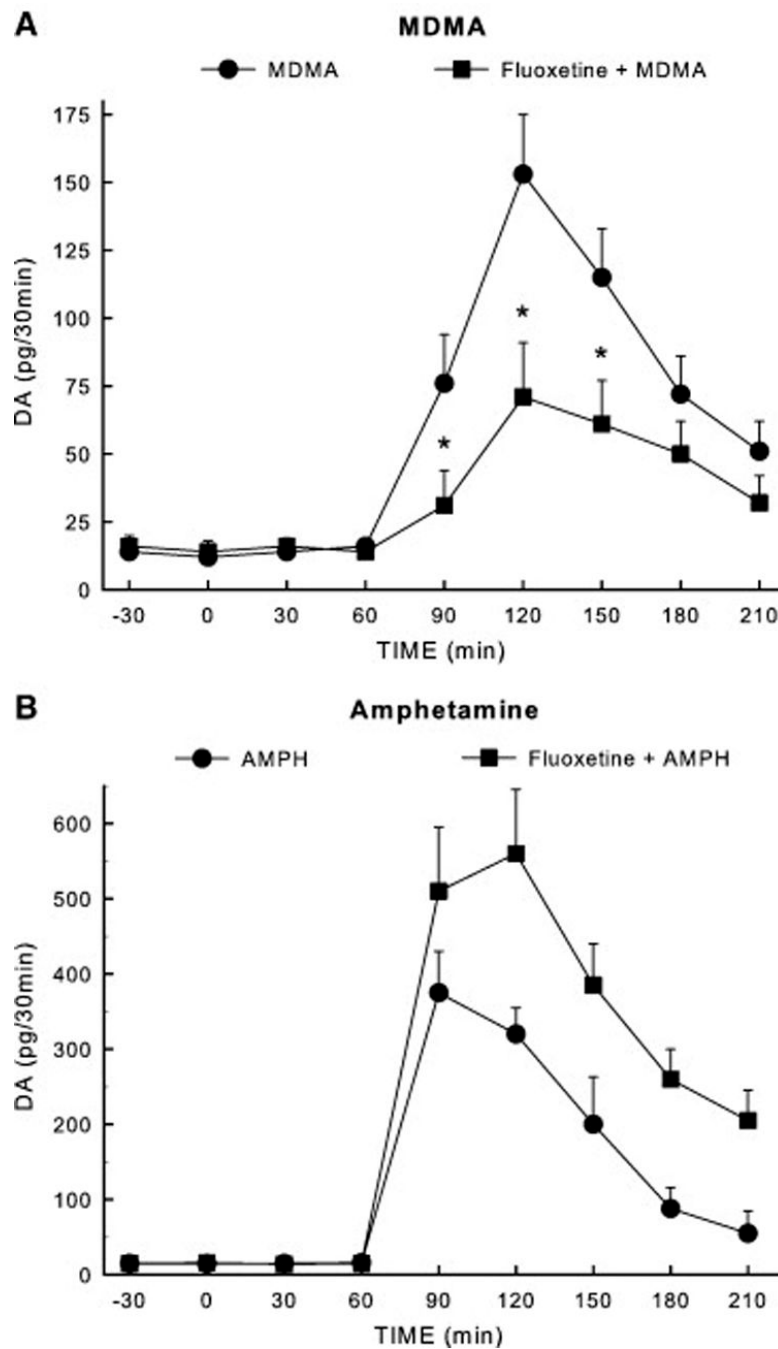
Figure 1.
Differential effect of fluoxetine on MDMA-and amphetamine-induced dopamine release in the striatum. Fluoxetine (10 mg/kg, ip) or vehicle was administered at time 0, and MDMA (10 mg/kg) (panel A) or amphetamine (AMPH, 5 mg/kg) (panel B) was injected ip at time 60 minutes. Data are the mean ± SEM of 6–9 rats.
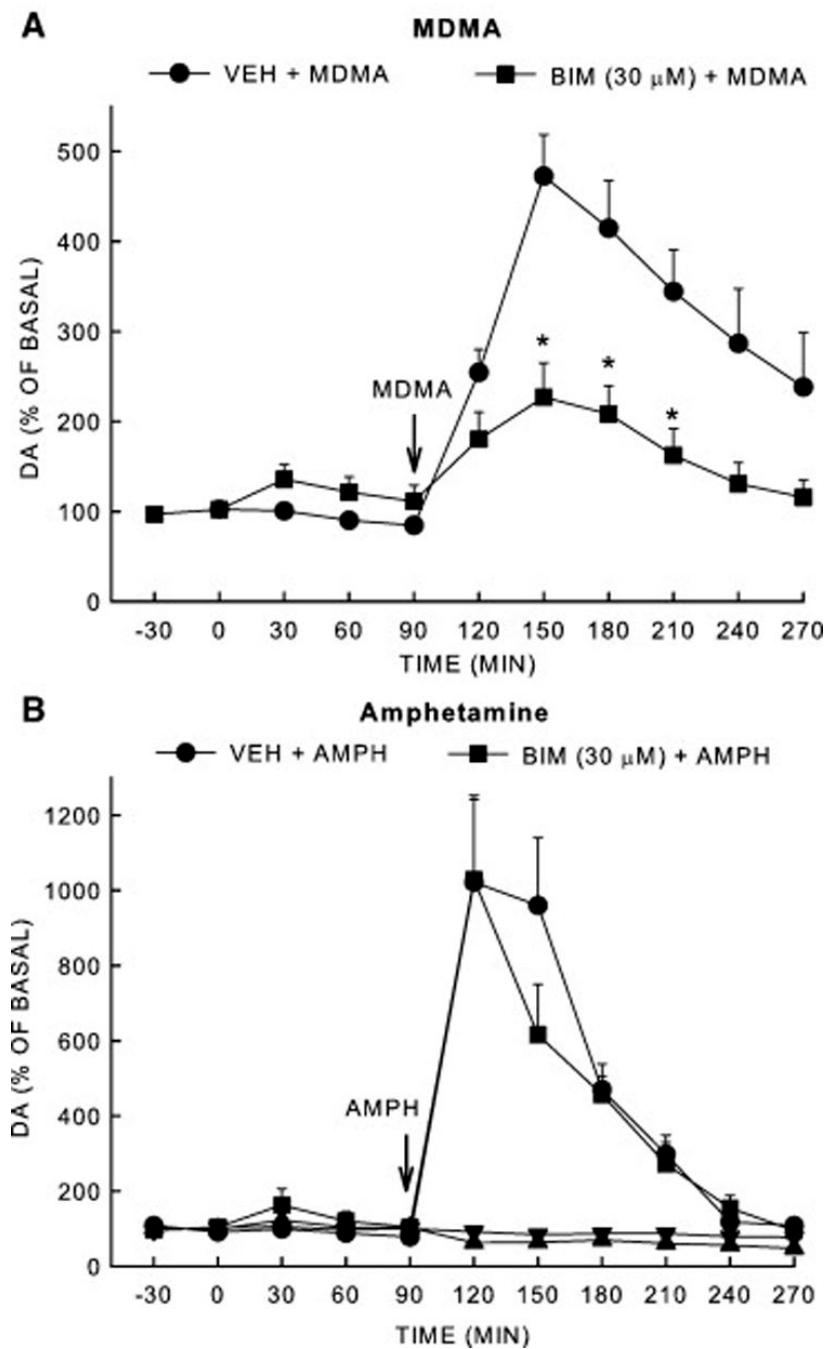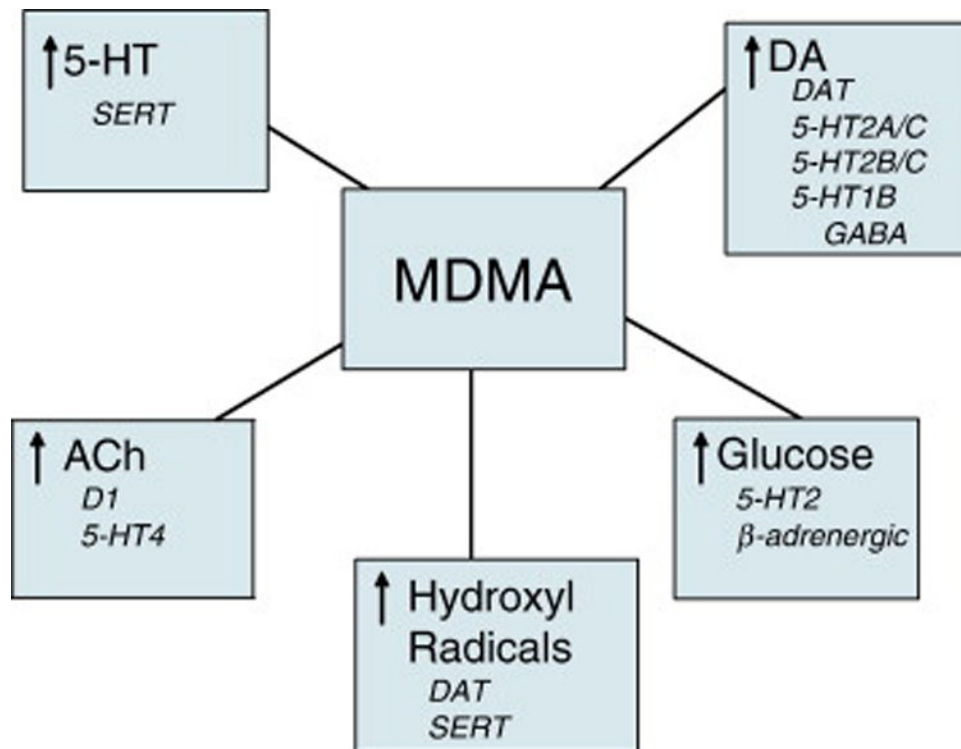
Figure 2.
Differential effect of protein kinase C inhibition on MDMA- and amphetamine-induced DA release in the striatum. Bisindoylmaleimide (BIM, 30 µM) was perfused into the striatum beginning 90 minutes prior to the administration of MDMA (10 mg/kg, ip) (panel A) or amphetamine (5 mg/kg ,ip) (panel B). Values represent the means ± SEM of 6–9 rats. *Indicates values that are significantly (P<0.05) less than those for animals given only MDMA.
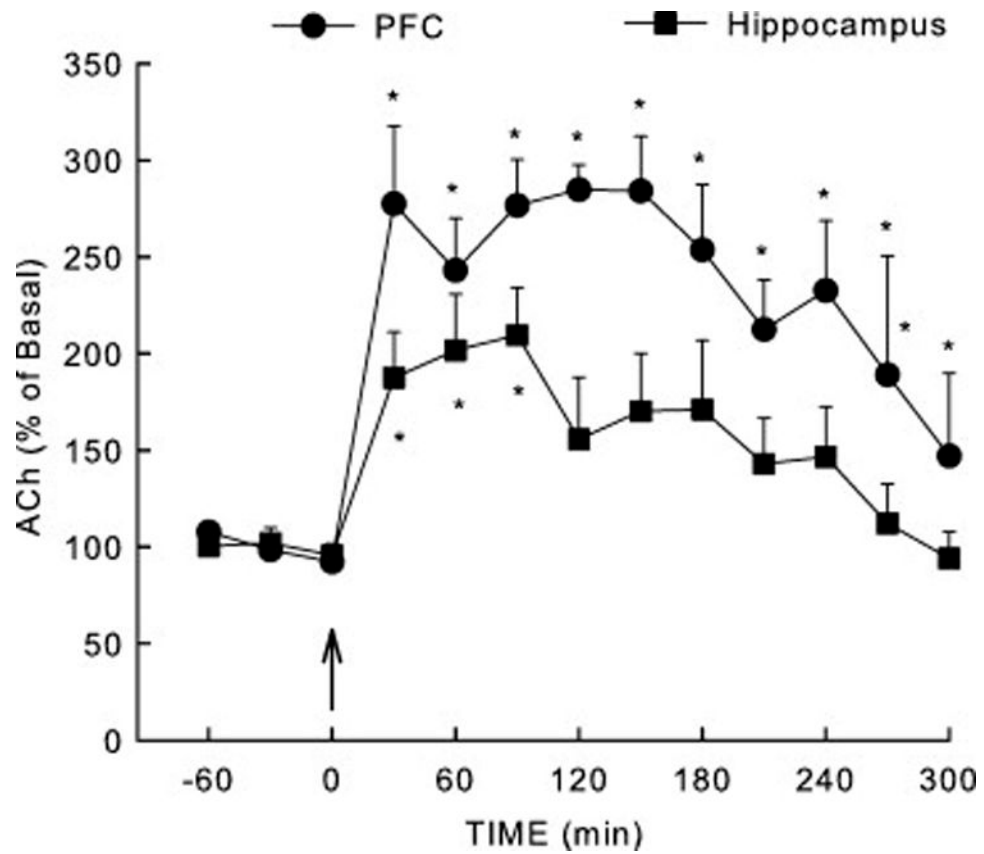
Figure 3.
Effect of MDMA on acetylcholine release in the prefrontal cortex and hippocampus. Rats received MDMA (10 mg/kg, ip) at time 0. N=6–12 rats/group. *Indicates values that are significantly (P<0.05) greater than baseline values.

Figure 4.
Diverse pharmacology of MDMA. The schematic summarizes findings from microdialysis studies in which the ability of MDMA to increase the extracellular concentrations of 5-HT, dopamine (DA), acetylcholine (ACh), glucose and hydroxyl radicals has been demonstrated. The neurochemical substrates depicted in italics indicate the receptors/transporters that mediate or modulate the respective effects of MDMA. Through its interactions with the 5-HT transporter (SERT) MDMA increases the extracellular concentration of 5-HT in multiple brain regions. MDMA-induced increases in extracellular 5-HT subsequently modulate the magnitude of transporter-mediated DA release evoked by MDMA in the striatum, prefrontal cortex and n. accumbens. The serotonergic modulation of DA release in the striatum and n. accumbens occurs through 5-HT receptor dependent decreases and increases in GABA release in the substantia nigra and ventral tegmental area, respectively. MDMA also increases the extracellular concentration of ACh in the prefrontal cortex and hippocampus, and the cortical cholinergic response is mediated by both D1 and 5-HT4 receptors. Extracellular glucose also is increased in multiple brain regions following treatment with MDMA, and this response is dependent upon both 5-HT2 and β-adrenergic receptor stimulation. Finally, MDMA promotes the formation of hydroxyl radicals, as evidenced by the formation 2,3-dihydroxybenzoic acid. The generation of hydroxyl radicals and subsequent neurotoxicity to 5-HT terminals is dependent upon the actions of MDMA on both DAT and SERT.