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Short communication

Memantine prevents MDMA-induced neurotoxicity

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Abstract

MDMA (ecstasy) is an illicit drug causing long-term neurotoxicity. Previous studies demonstrated the interaction of MDMA with alpha-7 nicotinic acetylcholine receptor (nAChR) in mouse brain membranes and the involvement of alpha-7 nicotinic acetylcholine receptors (nAChR) in dopaminergic neurotoxicity induced by MDMA in mice. The aim of the present study was to investigate the utility of memantine (MEM), an alpha-7 nAChR antagonist used for treatment of Alzheimer's disease patients, to prevent neurotoxicity induced by MDMA in rats and the oxidative effect of this amphetamine derivative in mice striatal synaptosomes.

In isolated mouse striatal synaptosomes (an *in vitro* model of MDMA neurotoxicity of dopaminergic origin), MDMA (50 μM)-induced reactive oxygen species (ROS) production that was fully inhibited by MEM (0.3 μM). This effect of MEM was fully prevented by PNU 282987 (0.5 μM), a specific agonist of alpha-7 nAChR. The preventive effect of MEM on this oxidative effect can be attributed to a direct antagonism between MDMA (acting probably as agonist) and MEM (acting as antagonist) at the alpha-7 nAChR.

In Dark Agouti rats (an *in vivo* model of MDMA neurotoxicity of serotonergic origin), a single dose of MDMA (18 mg/kg) induced persistent hyperthermia, which was not affected by MEM pre-treatment. [^{3}H]Paroxetine binding (a marker of serotonergic injury) was measured in the hippocampus of animals killed at 24 h and 7 days after treatment. MDMA induced a significant reduction in [^{3}H]paroxetine binding sites at both times of sacrifice that was fully prevented by pre-treatment with MEM.

Since previous studies demonstrate that increased glutamate activity is not involved in the neurotoxic action of MDMA, it can be concluded that the effectiveness of MEM against MDMA-induced neurotoxicity would be the result of blockade of alpha-7 nAChR, although an indirect mechanism based on the interplay among the various neurotransmission systems leading to an increase in basal acetylcholine release should also be taken into account.

Keywords: MDMA; Ecstasy; Memantine; Mice; Dark Agouti rat; Neurotoxicity

3,4-Methylenedioxymethamphetamine (MDMA), also known as ''ecstasy'', is an illicit recreational drug. Its use is especially popular at dance parties (''raves''). Single administration of MDMA to rats and mice produces a rapid and sustained hyperthermia (that is dependent on ambient temperature) while its repeated administration produces long-term deficits known as neurotoxicity (for review see Green et al., 2003).

It is well known that neurotoxic effects of MDMA are species-dependent. In rats, MDMA is a selective serotonergic neurotoxin. In rats, administration of a neurotoxic regimen of this amphetamine derivative results in decreases in cerebral tissue concentrations of serotonin and decreases in serotonin uptake sites. This was only observed in a number of brain regions known to receive projections of serotonergic neurons, specially hippocampus and cerebral cortex (Battaglia et al., 1991). These deficits are evidenced, among others, by a decrease in the density of serotonin plasmalemmal transporter (SERT) labeled by [^{3}H]paroxetine (Battaglia et al., 1987) without glial activation (Pubill et al., 2003; Baumann et al., 2007; Straiko et al., 2007). Few studies about neuroprotection from MDMA neurotoxicity in Dark Agouti rats have been published. This rat strain is devoid of some CYP isoforms and is characterized by its high sensitivity for MDMA (O'Shea et al., 1998).

In mice, it is generally agreed that MDMA is a relatively selective dopaminergic neurotoxin, which produces

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a dopaminergic terminal injury and a sustained loss of dopamine in the striatum. As increased ROS formation is responsible for MDMA-induced neurotoxicity (Cadet et al., 2001), ROS formation in mice striatal synaptosomes is a useful index of MDMA-induced dopaminergic neurotoxicity (Chipana et al., 2006).

Previous works from our group described the interaction of MDMA with alpha-7 nicotinic acetylcholine receptor (nAChR) in mouse brain membranes and the involvement of this nAChR in the oxidative effect of MDMA in isolated synaptosomes from mouse striatum. Furthermore, methyllycaconitine (MLA), a specific antagonist of alpha-7 nAChR, significantly prevented, *in vivo*, MDMA-induced dopaminergic neurotoxicity in mice (Chipana et al., 2006). To our knowledge, no data about the involvement of alpha-7 nAChR in the serotonergic neurotoxicity induced by MDMA has been described. The aim of this paper is to study the utility of an alpha-7 nAChR antagonist with therapeutic relevance, such as memantine (MEM), as a useful drug to prevent MDMA-induced serotonergic neurotoxicity in rats and the oxidative effect of this amphetamine derivative in mice striatal synaptosomes.

MEM, a non-competitive antagonist of the NMDA receptor, is a useful drug used in the treatment of patients with moderate-to-severe Alzheimer's disease by reducing the tonic, but not synaptic, NMDA receptor activity (Reisberg et al., 2003). In the cerebrospinal fluid of patients receiving the recommended maintenance dose of 20 mg/day of MEM, concentrations as high as 1 μM may be reached in the extracellular brain compartment (Danysz and Parsons, 2003). Results of Creeley et al. (2006) are consistent with previous research with regard to the threshold for conferring neuroprotection in that they found that a 20 mg/kg dose was required for MEM to begin to produce an anti-excitotoxic neuroprotective effect. When MEM is administered to rats at a single dose for behavioral assays, a dose between 1 and 10 mg/kg is usually used (Peeters et al., 2003; Bale et al., 2005).

More recently, some authors have associated MEM with alpha-7 nicotinic receptors (nAChR). Aracava et al. (2005) demonstrated that MEM, at clinically relevant concentrations, blocked in a non-competitive manner alpha-7 nAChR (IC_{50} value of 0.34 μM) more potently than NMDA receptors (IC_{50} value of 5.1 μM). It must be noted that a MEM IC_{50} value of 1–3 μM for NMDA receptors has been reported by other authors (Parsons et al., 1999). According with Aracava et al., MEM interacts with more than one class of sites on the alpha-7 nAChRs. One is voltage-sensitive, and therefore, likely to be within the receptor channel. The other is voltage-insensitive, and therefore, likely to be in the extracellular domain of the receptor.

Here, in the *in vivo* experiments, we have used MDMA administered to Dark Agouti rats as a model of serotonergic neurotoxicity and, in the *in vitro* experiments, a mice striatal synaptosome model has been used to study MDMA-induced ROS production thereby avoiding effects on body temperature. This *in vitro* model also allows the study of the direct effect of MDMA on dopamine terminals without interference with glutamate or glial mechanisms.

Our hypothesis, derived from our previous results, is that MEM can prevent serotonergic neurotoxicity induced by MDMA administration to rats and also the oxidative effect of this amphetamine derivative in mice striatal synaptosomes, which is due to dopamine oxidation. In this paper, we demonstrate that MEM inhibits the loss of [^{3}H]paroxetine binding sites induced by MDMA in Dark Agouti rats and also inhibits MDMA-induced ROS production in mouse striatal synaptosomes, which confirm our hypothesis.

1. Methods

Effort was made to minimize the number as well as the suffering of animals used in this study. All experimental protocols regarding the use of animals (rats and mice), in this study, were approved by the Animal Ethics Committee of the University of Barcelona under the supervision of the Autonomous Government of Catalonia, and in accordance with guidelines of the European Communities Council (86/609/ECC).

1.1. In vitro model of dopaminergic neurotoxicity: mouse striatal synaptosomes

Purified striatal synaptosomes were obtained as described previously (Chipana et al., 2006; Pubill et al., 2005) from male Swiss CD-1 mice. Synaptosome fraction was diluted in HEPES-buffered solution (HBSS) (composition in mM: 140 NaCl, 5.37 KCl, 1.26 $CaCl_2$, 0.44 KH_2PO_4, 0.49 $MgCl_2{\cdot}H_2O$, 0.41 $MgSO_4{\cdot}7H_2O$, 4.17 $NaHCO_3$, 0.34 $Na_2HPO_4{\cdot}7H_2O$, 5.5 glucose and 20 HEPES-Na), to a final protein concentration of about 0.1 mg/ml and was splitted in tubes (1 ml of synaptosomal suspension/tube). The formation of intrasynaptosomal ROS was measured using 2′,7′-dichlorofluorescein diacetate (DCFH-DA)(Molecular Probes, Leiden, The Netherlands). DCFH-DA (50 μM) was added to each tube, together with test drugs at the appropriate concentrations. Drugs were dissolved in bi-distilled water and added at a volume of 10 μl to each ml of synaptosomal preparation.

The synaptosomes were incubated for 15 min in a shaking bath at 37 °C in the dark and thereafter MDMA (National Health Laboratory, Spain) was added. Incubation was continued in the dark for the desired time and finally stopped by centrifugation at 13,000 × *g* for 30 min at 4 °C. The pellets were resuspended in 1 ml ice-cold Tris–sucrose buffer (320 mM) and recentrifuged. The final pellets were resuspended in 0.2 ml of cold HBSS and the tubes were kept on ice in the dark until fluorescence measurements were performed, within the hour. Fluorescence measurements were performed on a Coulter Epics XL-MCL flow cytometer equipped with an argon laser. The excitation wavelength was 488 nm and the emission was detected at 525 nm.

The possibility of a non-specific antioxidant effect for test compounds was assessed against ROS induced by 100 μM H_2O_2 in synaptosomes incubated under the same conditions described above.

Values were taken from triplicates of each experimental condition, and individual experiments were performed at least three times. Mean fluorescence values of each experimental condition are expressed as percentages of control (100%). All data are expressed as mean ± standard error of the mean (S.E.M.). Differences between groups were compared using one-way analysis of variance (ANOVA, two-tailed). Significant ($p < 0.05$) differences were then analyzed by Tukey's post hoc test for multiple means comparisons where appropriate.

1.2. In vivo experiments for serotonergic neurotoxicity assessment

For *in vivo* experiments, male Dark Agouti rats were used. This rat strain only requires a single dose of MDMA to produce a significant serotonergic lesion (O'Shea et al., 1998), in contrast to Sprague–Dawley or Wistar rats, which usually require several doses to produce a similar injury (Battaglia et al., 1987).

The MDMA group received a dose of 18 mg/kg, s.c. The MEM + MDMA group received a dose of MEM (Lundbeck Lab., Denmark) (5 mg/kg, i.p.) 30 min before the corresponding dose of MDMA. There were also two more groups: one received saline (1 ml/kg) and the other received MEM alone at the same dose as above. During the experiments, animals were maintained in an ambient temperature of 26 ± 2 °C and were kept under these conditions until 1 h after treatment. Body temperature was measured at 1 and 3 h after drug treatment using a rectal probe. To quantify SERT, animals were killed at 1 and 7 days after treatment, and their hippocampus were quickly dissected out for [^{3}H]paroxetine binding studies (Camarasa et al., 2006).

Briefly, SERT density in rat hippocampal membranes was quantified by measuring the specific binding of 0.05 nM [^{3}H]paroxetine (Perkin-Elmer Life Sci., Boston, USA) after incubation with 150 μg of protein at 25 °C for 2 h in a Tris–HCl buffer (50 mM, pH 7.4), containing 120 mM NaCl and 5 mM KCl to a final volume of 1.6 ml. Clomipramine (Sigma Chem. Co.) (100 μM) was used to determine non-specific binding. Specific binding was defined as the difference between the radioactivities measured in the absence (total binding) and in the presence (non-specific binding) of an excess of non-labeled ligand. Incubation was finished by rapid filtration under vacuum through GF-51 glass fibre filters (Schleicher and Schuëll, Dassel, Germany). Tubes and filters were washed rapidly three times with 4 ml of ice-cold buffer, and the radioactivity in the filters was measured using a liquid scintillation counter (Packard, Tri-Carb 2100TR).

2. Results

In mouse isolated striatal synaptosomes, MDMA (50 μM)-induced ROS production that was fully inhibited by MEM (0.3 μM). At the concentration used, MEM had no effect on hydrogen peroxide-induced ROS (data not shown), ruling out a non-specific antioxidant effect of this drug. Moreover, MEM (0.3 μM) was devoid of effect when it was present alone in the preparation. The inhibitory effect of MEM on ROS production induced by MDMA was fully prevented by PNU 282987 (0.5 μM), a specific agonist of alpha-7 nAChR (Fig. 1). PNU 282987 alone, at the same concentration, did not affect basal ROS production (100.93 ± 0.62%, n.s. *vs.* saline group) as its association with MEM 0.3 μM (100.62 ± 0.54%, n.s. *vs.* saline group). Also no additive effect was found between MDMA (50 μM) and PNU 282987 (0.5 μM).

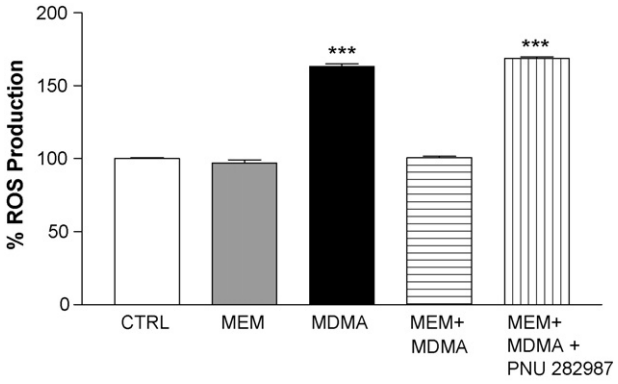

Fig. 1. Effect of MEM on MDMA-induced ROS production in mouse striatal synaptosomes. ROS were measured in the absence (CTRL), or the presence of MDMA (50 μM) alone or in combination with MEM (0.3 μM) and PNU 282987 (0.5 μM). Results are expressed as means ± S.E.M. from at least three separate experiments run on triplicates. $^{***}p < 0.001$ *vs.* CTRL.

Results from *in vivo* treatments demonstrated that in Dark Agouti rats, a single dose of MDMA induces persistent hyperthermia (see Table 1). This effect was not affected by MEM pre-treatment. Additionally, [^{3}H]paroxetine binding was measured in the hippocampus of animals killed at 24 h and 7 days after treatment. In the hippocampus of MDMA-treated rats, there was a significant reduction in [^{3}H]paroxetine binding sites at both times of sacrifice. This reduction was fully prevented by pre-treatment with MEM. Furthermore, treatment with MEM alone had no effect on [^{3}H]paroxetine binding sites (Table 1).

3. Discussion

Results obtained in the present work confirm our initial hypothesis that MEM prevents MDMA-induced neurotoxicity. In this paper, we provide first evidence that MEM, at a low dose, prevents the dopamine-dependent oxidative effect (*in vitro*) and serotonergic neurotoxicity (*in vivo*) induced by MDMA in mice and rats, respectively. This is the first report for a neuroprotective effect against MDMA-induced neurotoxicity of a drug used in clinical practice, having a mechanism of action focused in its capacity to block alpha-7 nAChR.

Present results demonstrate that MDMA increases DCFH-DA fluorescence when added to mouse striatal synaptosomes, indicating that it induces ROS production inside synaptosomes, which probably is one of the main causes of selective dopaminergic terminal injury in mice. This ROS production is completely abolished by MEM and is fully recovered by the preincubation with PNU 282987. It should be pointed out that MEM prevents the ROS production induced by MDMA at a

Table 1
Effect of memantine on body temperature and on SERT density in rat hippocampus

Treatment	Rectal body temperature in °C (hours post-treatment) ($n = 8$)		[^{3}H]Parotexine binding sites in % ($n = 5$–7)	
	1 h	3 h	1 DPS[$]	7 DPS[$]
Saline	36.9 ± 0.2	37.0 ± 0.1	100.0 ± 2.6	100.0 ± 9.3
MDMA	39.1 ± 0.1[***]	39.1 ± 0.1[***]	62.2 ± 3.9[***]	70.0 ± 7.8[*]
Memantine	37.6 ± 0.1[*]	37.4 ± 0.1[*]	97.3 ± 0.9	116.4 ± 3.9
Memantine + MDMA	38.9 ± 0.1[***]	38.9 ± 0.1[***]	89.8 ± 2.6[###]	90.1 ± 6.2

Results are expressed as mean ± standard error of the mean.
One-way ANOVA followed by Tukey's test ([$]DPS: days post-treatment).
[*] $p < 0.05$.
[***] $p < 0.001$ *vs.* saline group.
[###] $p < 0.001$ *vs.* MDMA group.

concentration compatible with its potency blocking alpha-7 nAChR.

Our previous results demonstrated that MDMA displaced [^{3}H]MLA binding in mouse brain membranes with a K_i value of 27.45 ± 0.71 μM (Chipana et al., in press) and that MDMA-induced oxidative effect in mice striatal synaptosomes is blocked by MLA and alpha-bungarotoxin, both alpha-7 nAChR antagonists, but not by NMDA antagonists (Chipana et al., 2006; Escubedo et al., 2005). In agreement with these results and those obtained by Liu et al. (2003) this oxidative effect can be attributed, among others, to an interaction of MDMA with alpha-7 nAChR leading to its activation.

In a previous paper, using MLA and the same *in vitro* model, we have described that MDMA, inside dopaminergic terminals, displaces vesicular dopamine. Also MDMA, by binding to DAT, reverses its function, resulting in release of cytosolic dopamine. Additionally, at high concentrations, calcium entry (through alpha-7 nAChR activation by MDMA) triggers calcium-dependent mechanisms involved in DAT inhibition, such as protein kinase C or nitric oxide synthase (Chipana et al., in press). This inhibition traps dopamine inside terminal favoring, finally, its oxidation via MAO-B, and therefore, ROS production (Chipana et al., 2006). In agreement with results obtained in this previous paper with reserpine-treated animals and with EGTA, ROS production induced by MDMA is a consequence of a double mechanism: increase in cytosolic free dopamine and increase in cytosolic calcium.

Based on these mechanisms, we can deduce that the presence of an alpha-7 nAChR antagonist, as MEM, avoids the effect of MDMA on these receptors, preventing ROS production. These results provide us the first indication of a novel inhibitory effect of MEM on MDMA-induced ROS production in the mouse striatum.

MDMA impairs the thermoregulatory response. Hyperthermia, the most dangerous clinical symptom of MDMA intoxication in humans, is apparent at high ambient temperatures. At this environmental condition and in Dark Agouti rats, a single dose of MDMA induced a significant increase in body temperature lasting for at least 3 h. Hypothermia is neuroprotective against MDMA-induced damage, probably because free radical formation is reduced when the MDMA-induced hyperthermic response is prevented (Colado et al., 1998). MEM given alone produced a slight (although significant) increase in body temperature but when it was administered previously to MDMA, the hyperthermic response to the amphetamine derivative was not modified. As a consequence, a neuroprotective effect based on an antihyperthermic mechanism of MEM can be ruled out.

Because MDMA is a selective serotonergic neurotoxin in rats and humans (but dopaminergic in mice), we measured [^{3}H]paroxetine binding in the hippocampus of Dark Agouti rats. A significant decrease in the density of SERT was already found in the hippocampus of MDMA-treated rats at 24 h post-treatment and it was still present at 7 days post-treatment indicating a long-term neurotoxicity. This is the first time that such a rapid MDMA-induced loss in SERT is described in hippocampus, which is probably attributable to the major sensitivity of the rat strain used. In this brain area, MEM significantly prevented the loss in [^{3}H]paroxetine binding sites, suggesting a neuroprotective effect for serotonin terminals. Although MEM could prevent the MDMA-induced neurotoxicity as an antagonist of NMDA receptors, this hypothesis is not likely since in different *in vitro* studies of our group neither phencyclidine nor MK-801, both antagonists of the NMDA receptors, prevented the oxidative stress induced by MDMA (Chipana et al., 2006) nor the cellular death by amphetamine derivatives (Jiménez et al., 2004). Moreover, NMDA receptor antagonists are neuroprotective against MDMA-induced neurodegeneration only if they induce hypothermia and further suggest that increased glutamate activity is not involved in the neurotoxic action of MDMA (Colado et al., 1998).

Because increased free radical formation is also a key element in MDMA-induced serotonergic neurotoxicity in rats (Shankaran et al., 1999), it is probably that the effectiveness of MEM against MDMA-induced neurotoxicity, as in isolated mice synaptosomes, would be the result of blockade of alpha-7 nAChR. This is in agreement with recent results of Klingler et al. (2005) suggesting an agonistic action of MDMA on alpha-7 nAChR. Although the main hypothesis of MEM's neuroprotective effect is based on a direct antagonism between MDMA (acting probably as agonist) and MEM (acting as antagonist) at the alpha-7 nAChR, indirect mechanism based on the interplay among the various neurotransmission systems leading to a modification in basal ACh release should also be

taken into account. Nair and Gudelsky (2006) described a stimulatory effect of MDMA on hippocampal ACh release, which involves non-dopaminergic and non-serotonergic mechanisms. Furthermore, an additional *in vivo* antioxidative effect of MEM cannot be ruled out.

This communication represents the first paper describing a preventive effect of a clinically useful drug against MDMA-induced neurotoxicity. However, these are initial results and deserve to be followed up by more experimental studies on other species and/or strains, to explore the complete pharmacological profile of the interaction between MEM and MDMA and its potential use in the prevention of the cognitive impairment induced by the long-term abuse of amphetamine derivatives.

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References

Aracava Y, Pereira EFR, Maelicke A, Albuquerque EX. Memantine blocks alpha-7 nicotinic acethylcholine receptors more potently than *N*-methyl-D-aspartate receptors in rat hippocampal neurons. J Pharmacol Exp Ther 2005;312:1195–205.

Bale AS, Adams TL, Bushnell PJ, Shafer TJ, Boyes WK. Role of NMDA, nicotinic, and GABA receptors in the steady-state visual-evoked potential in rats. Pharmacol Biochem Behav 2005;82:635–45.

Battaglia G, Sharkey J, Kuhar MJ, de Souza EB. Neuroanatomic specificity and time course of alterations in rat brain serotonergic pathways induced by MDMA (3,4-methylenedioxymethamphetamine): assessment using quantitative autoradiography. Synapse 1991;8:249–60.

Battaglia G, Yeh SY, O'Hearn E, Molliver ME, Kuhar MJ, De Souza EB. 3,4-Methylenedioxymethamphetamine and 3,4-methylenedioxyamphetamine destroy serotonin terminals in rat brain: quantification of neurodegeneration by measurement of [^{3}H]paroxetine-labeled serotonin uptake sites. J Pharmacol Exp Ther 1987;242:911–6.

Baumann MH, Wang X, Rothman RB. 3,4-Methylenedioxymethamphetamine (MDMA) neurotoxicity in rats: a reappraisal of past and present findings. Psychopharmacology (Berl) 2007;189:407–24.

Cadet JL, Thiriet N, Jayanthi S. Involvement of free radicals in MDMA-induced neurotoxicity in mice. Ann Med Intern 2001;152:1S57–9.

Camarasa J, Pubill D, Escubedo E. Association of caffeine to MDMA does not increase antinociception but potentiates adverse effects of this recreational drug. Brain Res 2006;1111:72–82.

Chipana C, Camarasa J, Pubill D, Escubedo E. Protection against MDMA-induced dopaminergic neurotoxicity in mice by methyllycaconitine: involvement of nicotinic receptors. Neuropharmacology 2006;51:885–95.

Chipana C, García-Ratés S, Camarasa J, Pubill D, Escubedo E. Different oxidative profile and nicotinic receptor interaction of amphetamine and 3,4-methylenedioxy-methamphetamine. Neurochem Int, in press. (doi:10.1016/j.neuint.2007.07.016). July 28; [Epub ahead of print].

Colado MI, Granados R, O'Shea E, Green AR. Role of hyperthermia in the protective action of clomethiazole against MDMA (''ecstasy'')-induced neurodegeneration, comparison with the novel NMDA channel blocker AR-R15896AR. Br J Pharmacol 1998;124:479–84.

Creeley C, Wozniak DF, Labruyere J, Taylor GT, Olney JW. Low doses of memantine disrupt memory in adult rats. J Neurosci 2006;26:3923–32.

Danysz W, Parsons CG. The NMDA receptor antagonist memantine as a symptomatological and neuroprotective treatment for Alzheimer's disease: preclinical evidence. Int J Geriatr Psychiatry 2003;18:S23–32.

Escubedo E, Chipana C, Pérez-Sánchez M, Camarasa J, Pubill D. Methyllycaconitine prevents methamphetamine-induced effects in mouse striatum: involvement of α7 nicotinic receptors. J Pharmacol Exp Ther 2005;315:658–67.

Green AR, Mechan AO, Elliot JM, O'Shea E, Colado I. The pharmacology and clinical pharmacology of 3,4-methylenedioxymethamphetamine (MDMA, ''ecstasy''). Pharmacol Rev 2003;55:463–508.

Jiménez A, García E, Verdaguer E, Pubill D, Sureda FX, Canudas A, Escubedo E, Camarasa J, Camins A, Pallàs M. Neurotoxicity of amphetamine derivatives is mediated by caspase pathway activation in rat cerebellar granule cells. Toxicol Appl Pharmacol 2004;196:223–34.

Klingler W, Heffron JJ, Jurkat-Rott K, O'Sullivan G, Alt A, Schlesinger F, Bufler J, Lehmann-Horn F. 3,4-Methylenedioxymethamphetamine (ecstasy) activates skeletal muscle nicotinic acetylcholine receptors. J Pharmacol Exp Ther 2005;314:1267–73.

Liu PS, Liaw CT, Lin MK, Shin SH, Kao LS, Lin LF. Amphetamine enhances Ca^{2+} entry and catecholamine release via nicotinic receptor activation in bovine adrenal chromaffin cells. Eur J Pharmacol 2003;460:9–17.

Nair SG, Gudelsky GA. 3,4-Methylenedioxymethamphetamine enhances the release of acetylcholine in the prefrontal cortex and dorsal hippocampus of the rat. Psychopharmacology (Berl) 2006;184:182–9.

O'Shea E, Granados R, Esteban B, Colado MI, Green AR. The relationship between the degree of neurodegeneration of rat brain 5-HT nerve terminals and the dose and frequency of administration of MDMA ('ecstasy'). Neuropharmacology 1998;37:919–26.

Parsons CG, Danysz W, Quack G. Memantine is a clinically well-tolerated *N*-methyl-D-aspartate (NMDA) receptor antagonist—a review of preclinical data. Neuropharmacology 1999;38:735–67.

Peeters M, Maloteaux JM, Hermans E. Distinct effects of amantadine and memantine on dopaminergic transmission in the rat striatum. Neurosci Lett 2003;343:205–9.

Pubill D, Canudas A, Pallas M, Camins A, Camarasa J, Escubedo E. Different glial response against methamphetamine and methylenedioxymethamphetamine-induced neurotoxicity. Naunyn Schmiedeberg's Arch Pharmacol 2003;367:490–9.

Pubill D, Chipana C, Camins A, Pallas M, Camarasa J, Escubedo E. Free radical production induced by methamphetamine in rat striatal synaptosomes. Toxicol Appl Pharmacol 2005;204:57–68.

Reisberg B, Doody R, Stöffler A, Schmitt F, Ferris S, Möbius HJ. Memantine in moderate-to-severe Alzheimer's disease. New Engl J Med 2003;348:1333–41.

Shankaran M, Yamamoto BK, Gudelsky GA. Mazindol attenuates the 3,4-methylenedioxymethamphetamine-induced formation of hydroxyl radicals and long-term depletion of serotonin in the striatum. J Neurochem 1999;72:2516–22.

Straiko MM, Coolen LM, Zemlan FP, Gudelsky GA. The effect of amphetamine analogs on cleaved microtubule-associated protein-tau formation in the rat brain. Neuroscience 2007;144:223–31.