

Toxicity of amphetamines: an update

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Received: 24 January 2012/Accepted: 2 February 2012/Published online: 6 March 2012
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Abstract Amphetamines represent a class of psychotropic compounds, widely abused for their stimulant, euphoric, anorectic, and, in some cases, empathogenic, entactogenic, and hallucinogenic properties. These compounds derive from the /Lphenylethylamine core structure and are kinetically and dynamically characterized by easily crossing the blood-brain barrier, to resist brain biotransformation and to release monoamine neurotransmitters from nerve endings. Although amphetamines are widely acknowledged as synthetic drugs, of which amphetamine, methamphetamine, and 3,4-methylenedioxymethamphetamine (MDMA, ecstasy) are well-known examples, humans have used natural amphetamines for several millennia, through the consumption of amphetamines produced in plants, namely cathinone (khat), obtained from the plant *Catha edulis* and ephedrine, obtained from various plants in the genus *Ephedra*. More recently, a wave of new amphetamines has emerged in the market, mainly constituted of cathinone derivatives, including mephedrone, methylone, methedrone, and butylone, among others. Although intoxications by amphetamines continue to be common causes of emergency department and hospital admissions, it is frequent to find the sophism that amphetamine derivatives, namely those appearing more recently, are relatively safe. However, human intoxications

by these drugs are increasingly being reported, with similar patterns compared to those previously seen with classical amphetamines. That is not surprising, considering the similar structures and mechanisms of action among the different amphetamines, conferring similar toxicokinetic and toxicological profiles to these compounds. The aim of the present review is to give an insight into the pharmacokinetics, general mechanisms of biological and toxicological actions, and the main target organs for the toxicity of amphetamines. Although there is still scarce knowledge from novel amphetamines to draw mechanistic insights, the long-studied classical amphetamines—amphetamine itself, as well as methamphetamine and MDMA, provide plenty of data that may be useful to predict toxicological outcome to improvident abusers and are for that reason the main focus of this review.

Keywords Amphetamines • Amphetamine • Methamphetamine • 3,4-Methylenedioxymethamphetamine • Pharmacokinetics • Hyperthermia • Oxidative stress • Neurotoxicity • Cardiovascular toxicity • Hepatotoxicity • Rhabdomyolysis • Nephrotoxicity

Abbreviations

AMPH	Amphetamine
AUC	Area under the curve
C_{\max}	Maximum concentration
CNS	Central nervous system
COMT	Catechol-o-methyltransferase
CSF	Cerebrospinal fluid
CYP	Cytochrome P450
DA	Dopamine
DAT	Dopamine transporter
2,3-DHBA	2,3-Dihydroxybenzoic acid
DIC	Disseminated intravascular coagulation

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DMA	2.5-Dimethoxyphenylisopropylamine	N-Me-a-MeDA	A-methyl-a-methyldopamine,
DOM	2.5-Dimethoxy-4-methylphenylisopropylamine	NO*	3,4-Dihydroxymethamphetamine, HHMA
DOPAC	3,4-Dihydroxyphenylacetic acid	Or	Nitric oxide radical
EC ₅₀	Effective concentration 50%	ONOO ⁻	Superoxide anion
ETC	Electron respiratory chain	PET	Peroxynitrite
EU	European Union	PD	Positron emission tomography
fMRI	Functional magnetic resonance imaging	PK	Pharmacodynamic
GABA	Gamma-aminobutyric acid	PKC	Pharmacokinetic
GFAP	Glial fibrillary acidic protein	p.o.	Protein kinase C
GPX	Glutathione peroxidase	PMA	Per os
GR	Glutathione reductase	RNS	p-Methoxyamphetamine
GSH	Glutathione (reduced form)	ROS	Reactive nitrogen species
GST	Glutathione S-transferase	s.c.	Reactive oxygen species
/-GT	-/-Glutamyl transpeptidase or γ-glutamyltransferase	-SH	Subcutaneous
h	Hours	SPECT	Sulphydryl
5-HIAA	5-Hydroxyindoleacetic acid	SOD	Single-photon emission computed tomography
HMA	4-Hydroxy-3-methoxyamphetamine, 3-O-Me-a-MeDA	SULT	Superoxide dismutase
HMMA	4-Hydroxy-3-methoxymethamphetamine; 3-O-Me-N-Me-a-MeDA	t _{1/2}	Sulfotransferase
HO*	Hydroxyl radical	TH	Elimination half-life
5-HT	5-Hydroxytryptamine, Serotonin	THC	Tyrosine hydroxylase
5-HTT	Serotonin transporter; SERT	T _{max}	A ⁹ -T etrahy drocannabinol
HVA	4-Hydroxy-3-methoxyphenylacetic acid.	TPH	Median time to maximum concentration
	Homovanillic acid	UGT	Tryptophan hydroxylase
i.p.	Intraperitoneal	UK	UDP-glucuronosyltransferase
ICV	Intracerebroventricular	USA	United Kingdom
i.v.	Intravenous	VMAT	United States of America
Ke	Elimination constant	WT	Vesicular monoamine transporter
KO	Knockout		Wild type
LSD	Lysergic acid diethylamide		
MAO	Monoamine oxidase		
MAO _i	Monoamine oxidase inhibitor		
MDA	(±)-3,4-Methylenedioxymethamphetamine		
MDEA	Methylenedioxymethamphetamine		
MDMA	(±)-3,4-Methylenedioxymethamphetamine, "Ecstasy"		
a-MeDA	a-Methyldopamine, 3,4-Dihydroxyamphetamine, HHA		
METH	Methamphetamine		
4-MTA	4-Methylthioamphetamine		
mtDNA	Mitochondrial DNA		
MPT	Mitochondrial permeability transition		
NA	Noradrenaline		
NAC	N-Acetylcysteine		
NAT	Noradrenaline transporter		
NMDA	A-methyl-D-aspartic acid		

Introduction

Amphetamines are psychoactive substances with stimulant, euphoric, anorectic, and, in some cases, empathogenic, entactogenic, and hallucinogenic properties. The compounds with amphetaminic structure derive from the /J-phenylethylamine core structure (Fig. 1) and are kinetically and dynamically characterized by easily crossing the blood-brain barrier, to resist brain biotransformation and to release monoamine neurotransmitters from nerve endings. All the structural features that enable these physiological characteristics are present in the simplest derivative, amphetamine (AMPH) (Fig. 1). In fact, the presence of the a-methyl group on the AMPH molecule prevents the oxidation of the amine group by monoamine oxidase (MAO) enzymes and increases the ability to cross membranes that is enabled by their amphipathic nature (Young and Glennon 1986). In addition, due to the structural similarity with monoamine neurotransmitters, amphetamines act as competitive substrates at the membrane transporters of noradrenaline (NAT), dopamine (DAT), and serotonin

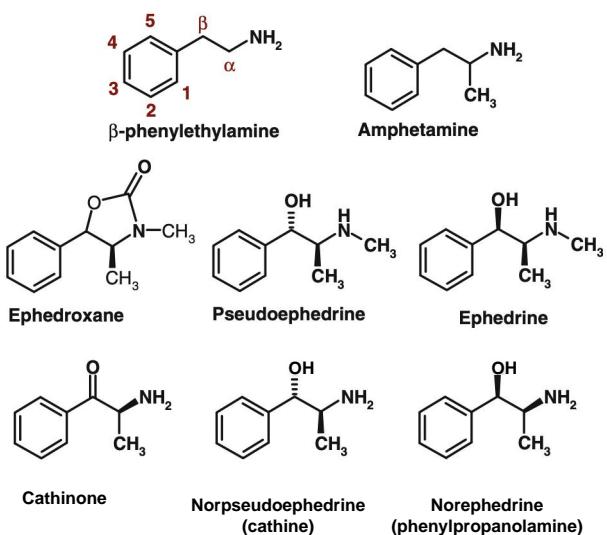


Fig. 1 Chemical structures of *β*-phenylethylamine (numbered) and amphetamine, as well as of the natural amphetamines ephedroxane, pseudoephedrine, ephedrine, cathinone, norpseudoephedrine (cathine), and norephedrine (phenylpropanolamine)

(5-HTT; SERT), reducing the reuptake of endogenous neurotransmitters, and inducing the reverse transport of endogenous neurotransmitters, and hence non-exocytotic neurotransmitter release. Amphetamines also promote dopamine (DA) and serotonin (5-HT) release from storage vesicles and prevent the uptake into vesicles, thus increasing the cytoplasmic concentrations of the neurotransmitter and making them more readily available for reverse transport (Capela et al. 2009; Green et al. 2003; Yamamoto et al. 2010).

Amphetamines are widely acknowledged as synthetic drugs. However, humans have used natural amphetamines for several millennia, through the consumption of amphetamines-producing plants, namely *Catha edulis* (Khat) and various plants in the genus *Ephedra* (family Ephedraceae), including *Ephedra sinica* (má huáng). Khat is an evergreen plant that grows at high altitudes in East Africa and Arabian Peninsula. Chewing its fresh leaves is a widespread habit in the local populations, with several million people consuming khat regularly in social sessions that often last for hours. Users of khat report increased levels of energy, alertness, and self-esteem, a sensation of elation, enhanced imaginative ability, and a higher capacity to associate ideas (Carvalho 2003). These effects have been attributed to the khat's content in cathinone, a potent natural amphetamine, although other less-potent amphetamines may also be present, namely norpseudoephedrine (cathine) and norephedrine (Fig. 1). One of the oldest medicinal herbs known to mankind is probably *Ephedra*, or ma huang as it is known in Traditional Chinese Medicine. The aerial parts of different *Ephedra* species contain at

least 6 optically active amphetamines (Fig. 1) concentrated in the internodes. The amphetamines ephedrine and pseudoephedrine are the main psychoactive constituents of the plant, the others being their optical isomers and N-methylated derivatives (Abourashed et al. 2003). Ephedroxane (Fig. 1), a less-known amphetamine, has also been isolated from the aerial parts of *Ephedra intermedia* and has been detected in at least 6 more species containing ephedrine alkaloids (Konno et al. 1979).

The amphetaminic structure allows the substitutions at the aromatic ring and at the α and /i carbons of the aliphatic chain and the amine terminal, to originate a wide range of amphetamines. Amphetamines without ring substitutions tend to be psychomotor stimulants, possessing sympathomimetic, antifatigue, and strong reinforcing effects in humans. Amphetamines with side-chain substitutions tend to be mainly psychomotor stimulants or anorectics; derivatives with terminal amine substitutions have psychomotor stimulant effects at low doses and hallucinogenic activity at higher doses (Young and Glennon 1986). As reviewed by Kleven and Seiden 1992, amphetamines with aromatic ring substitutions are usually weak stimulants, but some possess hallucinogenic activity (Kleven and Seiden 1992). Compounds such as 2,5-dimethoxyphenylisopropylamine (DMA), 2,5-dimethoxy-4-methylphenylisopropylamine (DOM), and 3,4,5-trimethoxyamphetamine all tend to exhibit a profile of sensory, behavioral, and physiological effects that are similar to lysergic acid (LSD). Amphetamines with methylenedioxy substitutions on the phenyl ring such as 3,4-methylenedioxymethamphetamine (MDMA) or 3,4-methylenedioxymphetamine (MDA) have both hallucinogenic and stimulant actions at relatively low doses and may represent a novel class of hallucinogens. The most representative examples of abused amphetamines are shown in Fig. 2.

More recently a wave of new amphetamines emerged mainly constituted of cathinone derivatives. There is the misconception that these compounds are "safe" as some of them are sold legally and are not controlled in many countries. For that reason, these drugs are so-called "legal highs". However, there are numerous case reports of toxicity similar to that seen with classical amphetamines (Karila and Reynaud 2011). Figure 3 depicts some of these new amphetamines.

The aim of the present review is to give an insight into the pharmacokinetics, general mechanisms of biological and toxicological actions, and the main target organs for toxicity of amphetamines. For this discussion, we selected two classical amphetamines: amphetamine and methamphetamine and the most popular amphetamine designer drug, MDMA. Hyponatremia, a characteristic toxic effect of MDMA, will not be included in this review as this subject has been thoroughly discussed elsewhere.

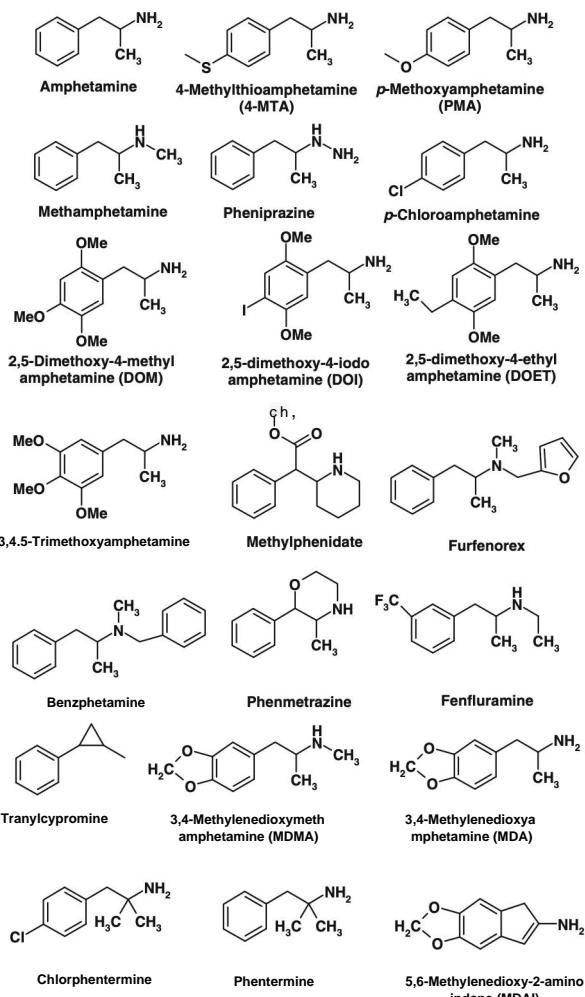


Fig. 2 Chemical structures of the most representative synthetic amphetamines

Pharmacokinetics

Pharmacokinetically, amphetamines are a very homogeneous group of drugs with high oral bioavailability, high volume of distribution (around 4 L/kg), and low plasma protein binding (usually less than 20%). Elimination half-life ranges between 6 and 12 h, and both renal and hepatic elimination occur. Though many amphetamines are extensively metabolized in the liver, for several of these drugs, a significant percentage is generally excreted without prior biotransformation (Kraemer and Maurer 2002).

Chemically, amphetamines are weak basic drugs (with pK_a values around 9.9) and have relatively low molecular weight. Therefore, these drugs can easily cross cellular membranes and lipidic layers, attaining high levels in tissues and biological fluids with pH lower than blood, including saliva and sweat (de la Torre et al. 2004a).

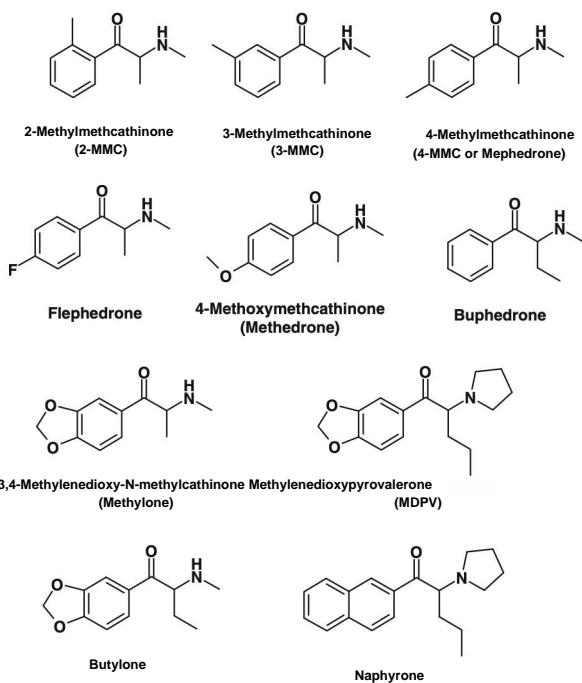


Fig. 3 Chemical structures of some representative examples of the so-called amphetamine-like legal highs

Main pharmacokinetic features of amphetamine, methamphetamine, and MDMA are summarized below.

Absorption

Amphetamine (AMPH) is usually consumed orally either as the S-(+)-enantiomer (d-amphetamine) or as the racemic mixture. Peak plasma concentrations (C_{max}) are generally attained within 4 h after ingestion, and both C_{max} and area under the plasma concentration-time curve over 24 h after administration (AUC₂₄) increase in a dose-dependent manner, with no significant differences between the two enantiomers (Angrist et al. 1987; Perez-Reyes et al. 1992; Pizarro et al. 1999) (Table 1).

Methamphetamine (METH) can be used by oral ingestion, intravenous injection, snorting, vapor inhalation, or smoking of the S-(+)-metamphetamine hydrochloride salt. The terminal plasma half-life is approximately 10 h for all administration routes and acute effects may persist up to 8 h after a single moderate dose (Cruickshank and Dyer 2009). As with intravenous injection (i.v.), smoked METH has a rapid onset of action. Maximum concentration (C_{max}) is usually attained between 1 and 2.5 h versus at least 3 h after oral administration (p.o.) (Harris et al. 2003; Mendelson et al. 1995; Perez-Reyes et al. 1991a, b; Schepers et al. 2003). Also, bioavailability is significantly higher for smoked METH compared to oral ingestion (up to 90 vs. 67%, respectively) (Cook et al. 1993). Bioavailability

Table 1 Pharmacokinetic parameters of amphetamine in humans after single oral administration

Dose (mg)	n	Isomer	CP _{max} (pg/L)	CU _{max} (pg/L)	tPmax (h)	tU _{max} (h)	AUC ₂₄ (pg·h/L)	Vd(L)	T _{1/2} (h)	Ae (%)	References
20	2	Racemate	(36.6–38.8) ^a		(3–2)		(482.5–131.6)				Pizarro et al. (1999)
30	2	Racemate	(57.3–57.8) ^a		(3–2)		(790.2–753.1)				
35	2	Racemate	(63.5–57.5) ^a		(2–2)		(822.9–758.6)				
40	11	Racemate	69.1 ± 5.7 ^b		2.2 ± 1.0		945.4 ± 71.8				
0.25 (mg/kg)	7	(S)	39.6 ± 2.8 ^b		3						Angrist et al. (1987)
0.5 (mg/kg)	8	(S)	67.3 ± 5.4 ^b		4						
0.06 (mg/kg)	12	(S)	18.3 ± 1.4 ^b		1.9 ± 0.2		49.4 ± 3.4 ^d				Perez-Reyes et al. (1992)
0.10 (mg/kg)	12	(S)	21.4 ± 0.7 ^b		2.5 ± 0.3		58.3 ± 2.3 ^d				
10 (with NaHCO ₃)	4	Racemate	20 ^f (S ^c)		4 ^f			237.6 ± 26.9	17.0 ± 1.5		Wan et al. (1978)
			20 ^f (R ^e)		4 ^f			243.4 ± 29.0 ^c	23.7 ± 3.5		
10 (with NH ₄ Cl)	4	Racemate	18 ^f (S ^c)		4 ^f			210.3 ± 51.3 ^c	6.8 ± 1.0		
			Racemate	17 ^f (R ^e)	4 ^f			248.1 ± 78.3 ^c	7.7 ± 1.0		
10 (with NaHCO ₃)	4	(S)	40 ^f		2.5 ^f			258.1 ± 32.7 ^c	15.6 ± 1.3		
10 (with NaHCO ₃)	4	(R)	40 ^f		3 ^f			267.4 ± 38.1 ^c	25.0 ± 2.3		
5 (with NH ₄ Cl)	7	(S)		1,635.7 ± 1091.0 ^b		4.9 ± 3.0				44.0 ± 6.7	Poklis et al. (1998)
10 (with NH ₄ Cl)	6	(S)		2,508.3 ± 493.1 ^b		5.3 ± 3.9				41.9 ± 4.8	
20 (with NH ₄ Cl)	7	(S)		3,308.6 ± 1212.5 ^b		9.7 ± 7.1				34.7 ± 5.2	

Adapted from (de la Torre et al. 2004a) and (Kraemer and Maurer 2002) and references therein

CP_{max} maximum plasma concentration; CU_{max} maximum urinary concentration; tPmax time to maximum plasma concentration; tU_{max} time to maximum urinary concentration; AUC₂₄ area under the plasma concentration-time curve from 0 to 24 h after administration; Vd volume of distribution; T_{1/2} terminal elimination half-life; Ae (%) amount excreted in 24-h urine collection expressed as % of ingested dose

^a n = 2 (individual values)

^b n > 2 (mean ± SD)

^c n > 2 (mean ± SEM)

^d AUC from 0 to 4 h after administration

^e Isomer studied

^f Approximate value

of snorted METH is about 79% with peak plasma concentrations attained after 4 h (Harris et al. 2003; Hart et al. 2008) (Table 2).

MDMA is usually ingested in single doses of 100–200 mg (1.4–2.8 mg/kg). However, many users repeatedly take the drug. Initial effects are noted after approximately 30 min (from 20 to 60 min), with maximal peak effects at 60–90 min after ingestion (Green et al. 2003). Drug effects parallel with plasma concentrations and last for approximately 6 h (Hegadoren et al. 1999). The pharmacological effects occur at 1–2 h after ingestion followed by a decrease to basal levels over a 4–6 h period (Mas et al. 1999).

Pharmacokinetic (PK) data reported for MDMA after a single per os (p.o.) administration in humans (de la Torre et al. 2000a; Fallon et al. 1999; Fowler et al. 2008; Helmlin et al. 1996; Mas et al. 1999; Mueller et al. 2009; Navarro et al. 2001; Pizarro et al. 2004; Samyn et al. 2002; Verebey et al. 1988) are summarized in Table 3. Several of these studies show that plasma C_{max} and $AUC_0-\infty$ increase in a dose-dependent manner for the 50, 75, 100 and 125 mg doses (de la Torre et al. 2000a; Mas et al. 1999). However, for the higher 150 mg dose, plasma levels were not proportional to the dose, suggesting non-linear PK at higher dose ranges (de la Torre et al. 2000a). These observations can be explained by the possible saturation of metabolic pathways and binding sites and by the inhibitory interaction of metabolites with some MDMA metabolizing enzymes (de la Torre et al. 2004a). The non-linear PK of MDMA has been confirmed in more recent and larger cohort studies (Fowler et al. 2008; Mueller et al. 2009). The urinary recovery of MDMA seems to be higher at lower doses which also agrees with non-linear PK (de la Torre et al. 2004b).

In spite of the observed high interindividual variability in the PK data described for MDMA, generally, after oral ingestion, peak plasma concentration is attained 1.5–3 h, as with most amphetamines (de la Torre et al. 2004a). The volume of distribution has been calculated as 452 ± 137 L (after the administration of a 125 mg dose) (de la Torre et al. 2004a), and the reported elimination half-life values, although varying substantially among studies, range between 8 and 9 h (de la Torre et al. 2004b).

After the oral administration of a racemic mixture, it was observed that the peak plasma R-(–)-MDMA enantiomer concentration was significantly higher, and the pharmacologically more active S-(+)-MDMA was more rapidly eliminated (Fallon et al. 1999; Pizarro et al. 2004). These differences observed with MDMA enantiomers in humans have been previously described after the administration of MDMA to rats (Fitzgerald et al. 1990).

The apparent lack of proportionality in the plasma concentrations expected after the administration of high MDMA doses, together with the general recognition that a large number of individuals ingest MDMA repeatedly, raises

serious concern with the possible potentiation of toxicity due to unexpectedly high plasma concentrations (de la Torre et al. 2004b). The results obtained at a controlled clinical study with the administration of two 100 mg MDMA doses in two separate administrations within 24 h to 9 individuals showed that after the ingestion of the second dose, the attained plasma concentrations could not be explained simply through drug accumulation, thus strongly indicating metabolic inhibition lasting over 24 h (Farre' et al. 2004). The same authors subsequently studied the influence of CYP2D6 genetic polymorphism on these PK parameters by genotyping the individuals that participated in the clinical study and calculating the respective PK data according to each of the CYP2D6-identified genotypes. The PK profile of MDMA varied according to the different genotypes (de la Torre et al. 2005). The data obtained in both studies are presented in Table 4.

Distribution

Amphetamines in general have low protein binding (usually under 20%), which confers high bioavailability to these drugs and favors their easy diffusion from the plasma to the extravascular compartment (de la Torre et al. 2004a). Amphetamine-dependent individuals seem to have larger volume of distribution and plasma elimination half-life relative to drug-naive individuals (6 vs. 4 L/kg), which is probably due to tissue sequestration as a result of the development of PK tolerance to the drug (Busto et al. 1989; de la Torre et al. 2004a). Protein binding and distribution volumes of S-(-)- and R-(–)-AMPH enantiomers are similar (Cook et al. 1993) (Table 1).

The distribution of METH is similar to that of AMPH and is apparently not significantly influenced by the route or time of administration (Mendelson et al. 1995; Shappell et al. 1996) (Table 2). Methamphetamine has been shown to accumulate in saliva, hair, and nails of drug abusers (Cook et al. 1993; Suzuki et al. 1989). In spite of the little contribution that this represents to the overall disposition of the drug, the monitoring of the drug in these non-conventional biological matrices is of clinical and forensic interest.

In a recent study, positron emission tomography (PET) was used to measure the whole-body distribution of METH in 19 individuals (9 Caucasians and 10 African Americans) (Volkow et al. 2010). These data showed that METH was highly accumulated in several organs, especially in the lungs, liver, and to a smaller extent in the brain and the kidneys. Interestingly, the lung accumulation of METH was 30% higher for the African American individuals, but did not differ in the other studied organs (Volkow et al. 2010). An earlier study conducted by the same team had already shown a fast (peak uptake at 9 min), widespread (with accumulation in cortical and subcortical brain regions and in white matter),

Table 2 Pharmacokinetic parameters of methamphetamine in humans

Dose (mg)	Route	n	Isomer	Bioavailability (%)	C _{max} (μg/L)	t _{max} (h)	AUC ₂₄ (pg·h/L)	Vd(L)	T _{1/2/p} (h)	CL _R (L/h)	Ae (%)	Reference
17.5	Smoked	6	(S)	90.3 ± 10.4	50 ^d	1–2 ^d	1,013.0 ± 141.0 ^{c,e}	3.2 ± 0.4 ^{c,h}	11.8 ± 1.4 ^c	6.7 ± 0.8 ^c	36.8 ± 4.3°	Cook et al. (1993)
12.4	i.v.	6	(S)		90 ^d	1–2 ^d	787.0 ± 29.7 ^{c,e}	3.7 ± 0.6 ^{c,h}	13.1 ± 1.5 ^c	6.9 ± 1.3 ^{c,f}	45.0 ± 9.5 ^{e,f}	Perez-Reyes et al. (1991b)
17.7	Vapor inhalation	6	Racemate		47.1 ± 5.6	2.5 ± 0.5						Mendelson et al. (1995)
24.1	i.v.	8	(S)		140 ^d	1.1 ^d		304.0 ± 26.0	12.0 ± 3.2	7.1 ± 2.1	38.7 ± 10.1 ^f	Perez-Reyes et al. (1991a)
10	Oral	6	Racemate		23 ^d	3.1 ± 0.3						Cook et al. (1992)
0.25 (mg/kg)	Oral	8	(S)			3.2			11.4	8.28		Shappell et al. (1996)
0.34 (mg/kg)	Oral	5	(S)	67 ± 3	94.1 ± 70.9 ⁱ	3.6 ± 0.6 ⁱ	599.1 ± 131.2 ^{s,i}	4.6 ± 1.4 ^h	9.1 ± 4.0	0.15 ± 0.06 ^h	19.9 ± 6.5	
0.34 (mg/kg)	Oral	5	(S)		60.4 ± 16.9 ⁱ	4.9 ± 2.4 ⁱ	469.7 ± 121.5 ^{s,i}	6.1 ± 2.6 ^h	10.8 ± 7.9	0.22 ± 0.08 ^h	22.8 ± 7.3	
50	Intranasal	8	(S)	79	113.0 ± 23.1	2.66 ± 1.16	2,000 ± 599 ^e		10.7 ± 2.39	102 ± 55.1	39.3 ± 24.5	Harris et al. (2003)
40	Smoked	8	(S)	67	50.9 ± 24.7	2.47 ± 3.91	801 ± 526		10.7 ± 2.11	98.9 ± 55.9	36.0 ± 17.7	
10	Oral	8	(S)		20.2 ± 6.4	5.4 ± 2.5	269.1 ± 94.3	5.8 ± 2.6 ^h	9.3 ± 3.7	32.2 ± 13.7		Schepers et al. (2003)
20	Oral	5	(S)		32.4 ± 7.7	7.5 ± 3.4	468.1 ± 151.8	5.3 ± 2.1 ^h	11.1 ± 7.2	33.5 ± 15.9		
15	i.v.	14	Racemate		49.1	0.53	370		9.4	37.3		Newton et al. (2005a, b)
30	i.v.	14	Racemate		109.0	0.51	684		9.91	43.2		

Adapted from (de la Torre et al. 2004a) and (Cruickshank and Dyer 2009)

C_{max}, maximum plasma concentration; t_{max}, time to maximum plasma concentration; AUC₂₄, area under the plasma concentration-time curve from 0 to 24 h after administration; Vd, volume of distribution; T_{1/2/p}, terminal elimination half-life; CL_R, renal clearance; Ae (%), amount excreted in 24-h urine collection expressed as % of ingested dose^a n = 2 (individual values)^b n > 2 (mean ± SD)^c n > 2 (mean ± SEM)^d Approximate value^e Parameter calculated from 0 to infinity^f Parameter calculated from 0 to 48 h^g Parameter calculated from 0 to 12 h^h Value expressed per kg bodyweightⁱ Parameters determined in serum

Table 3 Pharmacokinetic parameters of MDMA in humans after single oral administration

Dose (mg)	n	Isomer studied	C_{max} (μg/L)	t_{max} (h)	AUC_{24} (pg·h/L)	Vd/F(L)	$T_{1/2}(h)$	CL_r (L/h)	Ae (%)	% excreted dose	Reference
50	1		105.6	2					65	72	Verebey et al. (1988)
50	2		(19.8-82.8) ^a	(2-3)	(100.1-813.9)		(2.7-5.1)	(73.3 ^c -1.9)	(8.0-15.8)	(69.1-52.2)	de la Torre et al. (2000a, b)
75	8		130.9 ± 38.6 ^b	1.8 ± 0.4	1,331.5 ± 646.0		7.7 ± 3.2	12.8 ± 5.6 ^d	18.3 ± 3.5	53.7 ± 11.4	de la Torre et al. (2000a, b); Mas et al. (1999)
75	12		178 ± 52 ^b	2.0-4.0							Samyn et al. (2002)
100	2		189.9-209.7) ^a	(2-3)	(1,447.8-2,256.6)		(5.8-8.5)	(12.3-20.4)	(14.4-45.0)	(57.3-40.7)	de la Torre et al. (2000a, b)
100	8		181.4 ± 31.3 ^b	1.5	1,598.6 ± 733.3		7.2 ± 1.4				Navarro et al. (2001)
100	8		222.5 ± 26. ^b	2.3 ± 1.1				9.0 ± 2.3			de la Torre et al. (2004b)
100	4		181.6 ± 24.5 ^b	1.9 ± 0.2	1,465.9 ± 705.1		7.1 ± 1.3		15.0		Segura et al. 2001)
125	8		236.4 ± 58.0 ^b	2.4 ± 1.0	2,623.7 ± 572.9	452 ± 137	8.6 ± 3.2	13.0 ± 5.4 ^d	26.2 ± 10.7	51.0 ± 16.2	(de la Torre et al. (2000a, b); Mas et al. (1999))
150	2		(441.9-486.9) ^a	(1-5-2)	(5,132.8-5,232.0)		(6.9-7.2)	(5.2-11.3)	(20.6-43.0)	(37.3-54.7)	de la Torre et al. (2000a, b)
1.5 (mg/kg)	2		331	2							Helmlin et al. (1996)
1.6 (mg/kg)	9		254.7 ± 60.4 ^b	2.4 ± 0.6	3,070.6 ± 673.4		8.4 ± 1.6				Mueller et al. (2009)
1.0 (mg/kg)	17		162.9 ± 39.8 ^b	2.4 ± 0.6	1,833.2 ± 840.9 ^f	5.5 ± 1.1 ^g	6.9 ± 3.4	0.62 ± 0.19 ^b			Fowler et al. (2008)
1.6 (mg/kg)	17		291.8 ± 76.5 ^b	2.4 ± 0.7	3,485.3 ± 760.1 ^f	5.5 ± 1.3 ^g	8.1 ± 2.1	0.48 ± 0.1 1 ^h			
40	8	(R)	33.7 ± 14.9 ^b	4		383 ± 97	5.8 ± 2.2	10.5 ± 2.9	21.4 ± 11.6		Fallon et al. (1999)
		(S)	21.2 ± 10.8 ^b	2		595 ± 204	3.6 ± 0.9	10.2 ± 3.4	9.3 ± 4.9		
100	7	Racemate	208.7 ± 17. ^b	1.6 ± 0.4	3,108.5 ± 329.8 ^e		11.8 ± 4.4		22		Pizarro et al. (2004)
		(R)	116.7 ± 14.3 ^b	3.5 ± 2.2	2,158.8 ± 297.5 ^e		14.8 ± 9.2		16		
		(S)	88.8 ± 17.0 ^b	1.9 ± 0.5	773.0 ± 83.3 ^e		4.8 ± 1.7		7		

Adapted from (de la Torre et al. 2004a)

C_{max} , maximum plasma concentration; t_{max} , time to maximum plasma concentration; AUC_{24} , area under the plasma concentration-time curve from 0-24 h after administration; Vd volume of distribution; F systemic availability; $T_{1/2}$ terminal elimination half-life; CL_r renal clearance; Ae (%) amount excreted in 24-h urine collection expressed as % of ingested dose

^a n = 2 (individual values)^b n > 2 (mean ± SD)^c Total clearance: 86.9 ± 74.4 L/h and non-renal clearance: 74.0 ± 71.1^d Total clearance: 51.1 ± 14.1 L/h and non-renal clearance: 38.1 ± 13.3^e AUC from 0 to 48 h after administration^f AUC from 0 to oo^g Parameter calculated as L/kg^h Parameter calculated per L/h/kg

Table 4 Pharmacokinetic parameters of MDMA and metabolites in humans after repeated oral administration

Dose (mg)	CYP2D6 genotype	n	AUC ₀₋₂₄ (μg·h/L)	C _{max-0-24} (μg/L)	t _{max-0-24} (h)	AUC ₂₄₋₄₈ (μg·h/L)	C _{max-24-48} (μg/L)	t _{max-24-48} (h)	t _{1/2-24-48} (h)	AUC ₂₄₋₄₈ /AUC ₀₋₂₄	C _{max-24-48} /C _{max-0-24}	Reference	
MDMA ♀ × 100 mg	8 ^a	1,452 ± 771	180 ± 33	2 ± 0.26	7.0 ± 2.2	2,564 ± 762	232 ± 39	25.5 ± 0.33	8.8 ± 1.5	1.77	1.29	Faré et al. (2004)	
MCA ♂ × 100 mg	8 ^a	157 ± 55	11 ± 3	4 ± 6.88	12.8 ± 2.9	259 ± 81	15 ± 4	28 ± 2.71	14.1 ± 3.4	1.64	1.4	de la Torre et al. (2005)	
MDMA ♀ × 100 mg	*1/*4 *4/*4 *1/*1 *1/*4 *4/*4 *1/*1 *1/*4 *1/*4 *1/*1 *1/*4 *4/*4	8 ^a r ₁ - r ₂ - r ₃ - r ₄ - r ₅ - r ₆ r ₁ , r ₂ , r ₃ , r ₄ , r ₅ , r ₆ r ₁ , r ₂ , r ₃ , r ₄ , r ₅ , r ₆ r ₁ , r ₂ , r ₃ , r ₄ , r ₅ , r ₆ r ₁ , r ₂ , r ₃ , r ₄ , r ₅ , r ₆ r ₁ , r ₂ , r ₃ , r ₄ , r ₅ , r ₆ r ₁ , r ₂ , r ₃ , r ₄ , r ₅ , r ₆ r ₁ , r ₂ , r ₃ , r ₄ , r ₅ , r ₆ r ₁ , r ₂ , r ₃ , r ₄ , r ₅ , r ₆ r ₁ , r ₂ , r ₃ , r ₄ , r ₅ , r ₆	955.6 ± 243.8 2,446.0 ± 94.8 3113.9 2,065.9 ± 752.3 1,664.3 1,063.4 3,230.1 ± 428.3 2,033.8 ± 268.7 393.2	163.3 ± 26.3 214.3 ± 9.3 256.8 200.4 ± 95.7 104.1 79.8 362.1 ± 122.7 182.6 ± 18.4 57.6	1.75 ± 0.27 2.0 ± 0.29 2.0 1.0 ± 0.29 1.0 3.0 1.75 ± 0.68 1.88 2.0	6.0 ± 1.98 9.1 8.7 9.4 ± 1.56 25.5 15.1 8.3 ± 1.96 12.7 ± 1.81 14.8	212.5 ± 650.3 3,261.3 ± 414.2 4,256.4 1,580.9 ± 829.6 1,696.6 924.4 2,304.0 ± 382.2 1,545.6 ± 153.2 345.9	214.2 ± 29.9 269.1 ± 30.8 327.2 170.3 ± 85.1 95.0 65.2 158.6 ± 38.4 106.0 ± 12.9 44.5	25.5 ± 0.32 25.5 ± 0.29 25.75 25.5 ± 1.61 24.66 26.0 26.5 ± 0.92 26.75 ± 0.58 26.88	8.1 ± 1.5 10.1 ± 0.52 14.2 10.4 ± 2.70 35.1 19.5 20.7 ± 13.06 14.9 ± 2.85 15.0	2.3 1.3 1.4 0.8 1.02 0.9 0.7 0.76 0.88	1.3 1.3 1.3 0.85 0.9 0.8 0.4 0.58 0.8	Faré et al. (2004) de la Torre et al. (2005)

^a AUC₀₋₂₄ area under the plasma concentration-time curve from 0 to 24 h after the first administration; AUC₂₄₋₄₈ area under the plasma concentration-time curve during 24 h after the second administration (24–48 h); t_{max-0-24} time to maximum plasma concentration after the first administration; C_{max-0-24} maximum plasma concentration after the first administration; t_{1/2-0-24} elimination half-life after the first administration; t_{1/2-24-48} elimination half-life after the second administration

* Allele

and long-lasting distribution of METH in human brain, which parallels the long-lasting behavioral effects of the drug (Kolbrich et al. 2008). The study revealed no difference in METH pharmacokinetics and bioavailability between Caucasians and African Americans.

There are several reports on MDMA concentrations in several tissues and organs, determined in post-mortem studies. However, the ingested doses and the corresponding plasma concentrations attained in fatal intoxications are much higher than those reported in the clinical studies described before and that better agree with the recreational use of the drug. In Table 5, data from several representative studies are summarized. From the presented data, it can be concluded that MDMA accumulates in several tissues and organs, attaining much higher concentrations compared to those found in plasma, which can be up to 18 times higher in the liver (De Letter et al. 2004, 2006) and 30 times higher in the brain (Garcia-Repetto et al. 2003). The data presented in Tables 5 and 6 highlight the notorious interindividual variability in blood and organ MDMA concentrations.

Metabolism

Amphetamine is metabolized mainly through (1) N-deamination and oxidation into the corresponding benzoic acid derivatives that are further conjugated with glycine and excreted as the corresponding hippuric acids and (2) hydroxylation in position 4 of the aromatic ring, generating 4-hydroxyamphetamine, followed by conjugation of the phenol group with sulfate or glucuronic acid (Kraemer and Maurer 2002). During the hydroxylation step, AMPH can also form a reactive intermediate that can further react with glutathione to form the (glutathione-S-yl)-p-hydroxyamphetamine adduct (Carvalho et al. 1996). The minor metabolic pathway comprising the oxidation at the /-carbon of the side chain leads to the formation of norephedrine that is oxidized in the aromatic ring into hydroxynorephedrine (Caldwell 1980; Kraemer and Maurer 2002). Amphetamine N-deamination seems to be catalyzed by CYP450 isoenzymes of the CYP2C subfamily (Yamada et al. 1997), whereas CYP2D6 is involved in the hydroxylation of the aromatic ring (Bach et al. 2000) (Fig. 4).

The main metabolic reaction of METH is the N-demethylation into AMPH, which is mainly catalyzed by CYP2D6 (Bach et al. 1999; Lin et al. 1997). This isoenzyme also catalyses the 4-hydroxylation of the aromatic ring of METH producing primarily 4-hydroxymethamphetamine (Bach et al. 1999; Lin et al. 1997). The involvement of polymorphic CYP2D6 in the biotransformation of METH may partially contribute to interindividual variability in metabolism (Lin et al. 1997). /-Oxidation following N-demethylation produces norephedrine (Caldwell et al. 1972; Kraemer and Maurer 2002; Lin et al. 1997) (Fig. 4). Methamphetamine is

Table 5 MDMA blood and tissue concentrations found at autopsy after fatal intoxication

Blood mg/L (pM)	Liver ^d		Kidney ^d		Brain ^d		Bile ^d		Lung ^d		Heart ^d		Reference
	gg/g	Versus blood ratio	gg/g	Versus blood ratio	gg/g	Versus blood ratio	mg/L	Versus blood ratio	gg/g	Versus blood ratio	gg/g	Versus blood ratio	
2.8 ^c (14.5)	20.2	7.2			13.7	4.9							Rohrig and Prouty (1992)
0.58 ^c (2.99)	1.8	3.1											
0.18 (0.96)	13.23	71.5	9.82	53.1	12.79	69.2	27.34	147.8	10.7	57.9			Fineschi and Masti (1996)
2.9 (14.9)	6.4	2.2					73	25.2					Moore et al. (1996)
3.10 (16.0)	26.20	8.5	13.0	4.2	15.6	5.0	14.2	4.6	13.0	4.2	14.0	4.5	De Letter et al. (2002)
3.18 (16.5)	4.86	1.5					1.41	0.4					Garcia-Repetto et al. (2003)
0.28 (1.45)	5.13	18.3			8.42	30.1	1.23	4.4	2.64	9.4			
0.17 ^b (0.88)	0.18		0.05		0.14				1.46				Dams et al. (2003)
1.13 (5.8)	6.66	5.9	4.06	3.6	2.25	2.0	25.42	22.5	10.9	2.2	1.73	1.5	Sticht et al. (2003)
7.2 ^a (37.3)	29.7	4.1			29.1	4.0			36.6	5.1			
0.271 (1.4)	4.87	17.9	1.44	5.3	0.69	2.5	22.07	81.4	3.62	13.4	0.38	1.4	De Letter et al. (2004)
13.51 (70)	103.5	7.7	111.9	8.3			86.95	6.4	101.2	7.5	140.1	10.4	

^a mg/kg^b Determined before death^c Peripheral blood levels (femoral)^d Mean concentration values if different tissue portions were analyzed

metabolized to a lower extent than the methylenedioxymphetamine derivatives such as MDMA, and the urinary levels of unchanged METH are accordingly much higher (de la Torre et al. 2004a). In spite of retaining biological activity, the metabolites do not seem to contribute to the clinical effects of METH, since they are formed at low levels and at times at which acute effects are minimal (Cruickshank and Dyer 2009).

MDMA metabolism in humans is well documented and has been the subject of numerous reviews (de la Torre et al. 2004a, b; Kraemer and Maurer 2002). The first studies on MDMA metabolism were conducted by Lim and Foltz in 1988 elucidating MDMA metabolism in the rat, both *in vivo* and *in vitro*. These authors identified four main metabolic pathways in this species: (1) N-demethylation, (2) O-dealkylation (demethylenation), (3) deamination, and (4) methyl, glucuronide, and sulfate conjugation (Lim and Foltz 1988). The same authors would later identify the same metabolic pathways in humans (Lim and Foltz 1989).

In Fig. 5, the metabolic pathways for MDMA are schematically represented. MDMA metabolism has 2 major pathways: (1) the opening of the methylenedioxy ring followed by the methylation of one of the hydroxyl groups of the resulting catechol and/or the conjugation with glucuronide or sulfate (de la Torre et al. 2000a, 2004a; Lim and Foltz 1989; Maurer et al. 2000) and (2) the N-dealkylation into MDA that retains biological action (Johnson

et al. 1988). Subsequent deamination and side-chain oxidation leads to the formation of phenylketones followed by oxidation to benzoic acid derivatives (Maurer 1996) that are conjugated with glycine and excreted as hippuric acids (de la Torre et al. 2004b).

The opening of the methylenedioxy ring of both MDMA and MDA originates two catechol metabolites, N-methyl-a-methyldopamine (N-Me-a-MeDA) and a-methyldopamine (a-MeDA), respectively. This is the major metabolic pathway for MDMA in rat and in humans (Maurer et al. 2000). Both catechols are subsequently methylated by catechol-o-methyltransferase (COMT), preferentially at the hydroxyl group in position 4 of the aromatic ring. These monomethylated metabolites are mostly present in plasma and urine as conjugates with glucuronic acid and sulfate (de la Torre et al. 2000a, b; Kraemer and Maurer 2002; Maurer 1996). The catechol moiety confers high reactivity to these metabolites that easily oxidize into o-quinones (Cho et al. 1999). Quinones oxidation can also originate aminochromes (Bindoli et al. 1992) that further oxidize into melanin-like polymers (Zhang and Dryhurst 1994).

The redox cycles associated with these metabolic steps (Colado et al. 1997) originate reactive oxygen (ROS) and nitrogen (RNS) species that, such as the quinones, can attack important intracellular nucleophiles, including cysteine, glutathione (GSH), and protein sulfhydryl groups, and will eventually impair important macromolecules such as

Table 6 MDMA blood concentrations found at controlled clinical studies, non-fatal, and fatal intoxications

Dose	Number of pills	MDMA blood concentration (μg/L)	Study	Reference
50 ^a		105.6	Clinical study	Verebey et al. (1988)
50 ^{a,c}		(19.8–82.8)	Clinical study	de la Torre et al. (2000a, b)
75 ^{a,d}		130.9 ± 38.6	Clinical study	de la Torre et al. (2000a, b); Mas et al. (1999)
75 ^{a,d}		178 ± 52	Clinical study	Samyn et al. (2002)
100 ^{a,o}		(189.9–209.7)	Clinical study	de la Torre et al. (2000a, b)
100 ^{a,d}		181.4 ± 31.3	Clinical study	Navarro et al. (2001)
100 ^{a,d}		222.5 ± 26.1	Clinical study	de la Torre et al. (2004b)
100 ^{a,d}		208.7 ± 17.1	Clinical study	(Pizarro et al. 2004)
125 ^{a,d}		236.4 ± 58.0	Clinical study	de la Torre et al. (2000a, b); Mas et al. (1999)
150 ^{a,c}		(441.9–486.9)	Clinical study	de la Torre et al. (2000a, b)
	4	230	Non-fatal intoxication	Greene et al. (2003)
	5	350	Non-fatal intoxication	
	2	250	Non-fatal intoxication	
	2	130	Non-fatal intoxication	
	1	<100	Non-fatal intoxication	
100–150		7000 ^b	Non-fatal intoxication	Brown and Osterloh (1987)
	50	R(-) 44,000 ^b	Non-fatal intoxication	Ramcharan et al. (1998)
		S-(+) 42,000		
	42	7,720	Non-fatal intoxication	Randall (1992)
	18	4,050		Roberts and Wright (1993)
		1,100	Fatal intoxication	Dowling et al. (1987)
150	1.5	1,000	Fatal intoxication	
	1	424	Fatal intoxication	Chadwick et al. (1991)
		2,000	Fatal intoxication	Suarez and Riemersma (1988)
		2,400	Fatal intoxication	Greene et al. (2003)
		930	Fatal intoxication	
		2,800 ^f	Fatal intoxication	Rohrig and Prouty (1992)
		580 ^f	Fatal intoxication	
		180	Fatal intoxication	Fineschi and Masti (1996)
		2,900	Fatal intoxication	Moore et al. (1996)
		3,100 ^f	Fatal intoxication	De Letter et al. (2002)
		1090	Fatal intoxication	Garcia-Repetto et al. (2003)
	40	3,180	Fatal intoxication	
	170	280	Fatal intoxication	
		1,130 ^f	Fatal intoxication	Dams et al. (2003)
		7,200 ^e	Fatal intoxication	Sticht et al. (2003)
		271 ^g	Fatal intoxication	De Letter et al. (2004)
		1,3510 ^f	Fatal intoxication	

^a C_{max} ^b Approximately 4 h after ingestion^c n = 2 (individual values)^d n > 2 (mean ± SD)^e mg/kg^f Peripheral blood levels (femoral)^g Subclavian blood values

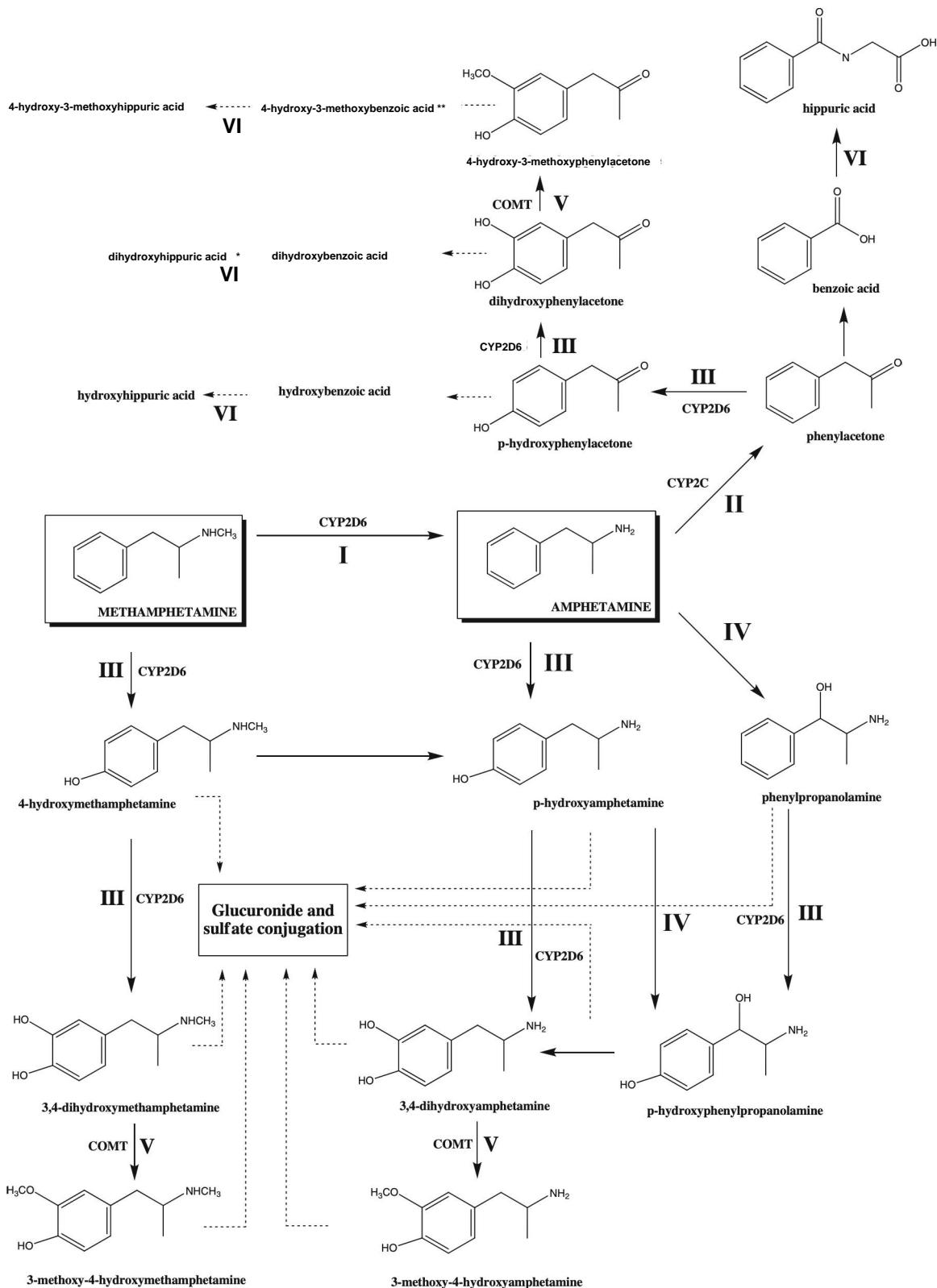


Fig. 4 Metabolic pathways of amphetamine and methamphetamine. I N-demethylation; II oxidative deamination; III aromatic hydroxylation; IV aliphatic hydroxylation; V O-methylation; VI glycine conjugation

proteins, lipids, and DNA (Bindoli et al. 1992; Bolton et al. 2000). These quinone metabolites can conjugate with GSH originating an adduct that can further conjugate with another GSH molecule, accompanied by the generation of ROS and RNS (Hiramatsu et al. 1990; Monks et al. 2004). The formation of these catechol conjugates with GSH was demonstrated in vitro in human liver microsomes, and it was shown in the same study that one of these adducts, the 5-(glutathione-S-yl)-a-MeDA, has central nervous system (CNS) activity after intracerebral administration in the rat (Easton et al. 2003). Also, the intracerebral administration of these adducts produced a significant depletion of serotonin in different rat brain areas, therefore showing that these adducts may be implicated in MDMA neurotoxic effects (Bai et al. 1999; Miller et al. 1997). More recently, the in vivo formation of these adducts was demonstrated in the brain of rats after subcutaneous injection of MDMA (Jones et al. 2005). In the same study, the serotonergic neurotoxicity of these metabolites was also observed (Jones et al. 2005).

Several in vitro studies have contributed for the demonstration of the toxicity of several MDMA metabolites by showing that the metabolic bioactivation of the drug has an important role in its neuronal (Capela et al. 2006a; Gollamudi et al. 1989; Patel et al. 1991), hepatic (Carvalho et al. 2004a, b), renal (Carvalho et al. 2002b), and cardiac (Carvalho et al. 2004c) toxicities.

In vivo studies in the rat revealed a third metabolic pathway consisting in the aromatic hydroxylation into trihydroxyamphetamine and trihydroxymethamphetamine that are highly neurotoxic (Lim and Foltz 1991; Zhao et al. 1992).

The cytochrome P450 isoenzymes are involved in the metabolic degradation of MDMA through the catalysis of the demethylation of the methylenedioxy ring with formation of N-Me-a-MeDA and a-MeDA and the N-demethylation into MDA. The in vitro demethylation of MDMA follows a biphasic Michaelis-Menten kinetics with a high-affinity and a low-affinity components (Kreth et al. 2000). The high-affinity component is catalyzed by CYP2D6, while the low-affinity component is mainly catalyzed by CYP1A2 and to a lower extent by CYP2B6 and CYP3A4 (Kreth et al. 2000; Maurer et al. 2000; Tucker et al. 1994). CYP2D6 contribution for MDMA demethylation was calculated to be around 50% in vitro in human liver and CYP2D6-expressing microsomes (Ramamoorthy et al. 2002; Tucker et al. 1994) and around 30% in vivo in humans (Segura et al. 2005). CYP2D6 demethylation is faster for the S-(+)-MDMA enantiomer compared to the R-(—)-MDMA enantiomer (Lin et al. 1997). The demethylation reaction can also occur without enzymatic catalysis through a spontaneous oxidation involving the hydroxyl radical (Kumagai et al. 1991; Lin et al. 1992; Maurer et al. 2000). In the rat, the demethylation reaction is catalyzed by the CYP2D1 and CYP3A2 isoenzymes (Maurer et al. 2000).

N-demethylation rate is around one order of magnitude lower than the demethylation rate and follows a monophasic kinetics, mainly catalyzed by CYP2B6 and also by CYP2D6, CYP1A2, and CYP3A4 in humans and by isoenzymes CYP1A2 and CYP2D1 in rats (Kreth et al. 2000; Maurer et al. 2000).

Table 7 summarizes the PK parameters of MDMA metabolites determined after MDMA administration in humans.

Excretion

The plasma half-life of amphetamines is, to a great extent, dependent on urine pH, since renal excretion is the main elimination pathway. In humans, AMPH and METH appear to follow one-compartment pharmacokinetics (Quinn et al. 1997). Given that these drugs are chemically weak bases, renal excretion increases with urine acidification and decreases with urine alkalization (Cook et al. 1993; Kim et al. 2004; Quinn et al. 1997). For this reason, there is wide variability in elimination half-life and often amphetamine abusers ingest bicarbonate to prolong the effect of the drug. Elimination half-life seems to be independent of the route of administration and tends to be longer in dependent AMPH and METH abusers (de la Torre et al. 2004a; Kidwell et al. 1998).

The fraction of the AMPH-administrated dose excreted without biotransformation in urine can vary between 3 and 55.5%, within a range of urinary pH from 5 to 8 (Cook et al. 1993). Due to its faster metabolism, the elimination half-life of the S-(+)-AMPH enantiomer is shorter than that of the R-(—)-AMPH enantiomer (Angrist et al. 1987) (Table 1).

Approximately 70% of a METH dose is excreted in urine within 24 h after administration. METH is mainly excreted unchanged (up to 50% of the dose) and as the 4-hydroxymetamphetamine (15%) and AMPH (10%) metabolites (Cook et al. 1993; Kim et al. 2004). Methamphetamine has an elimination half-life of 25 h and accumulates in urine with repeated dosing (Kim et al. 2004; Oyler et al. 2002). The fraction of unchanged METH excreted in urine decreases with increasing doses either due to a lower renal elimination rate or due to an increase in non-renal elimination rates at higher doses (Cook et al. 1993) (Table 2).

Amphetamines with the methylenedioxy substitution in the aromatic ring, like MDMA, are more extensively metabolized, and the amount excreted in urine without biotransformation is accordingly lower (de la Torre et al. 2004a).

Elimination half-life for MDMA ranges between 6 and 9 h (de la Torre et al. 2004a; Mas et al. 1999; Ramcharan et al. 1998), and most of the dose is excreted within the first 24 h after ingestion (Fallon et al. 1999).

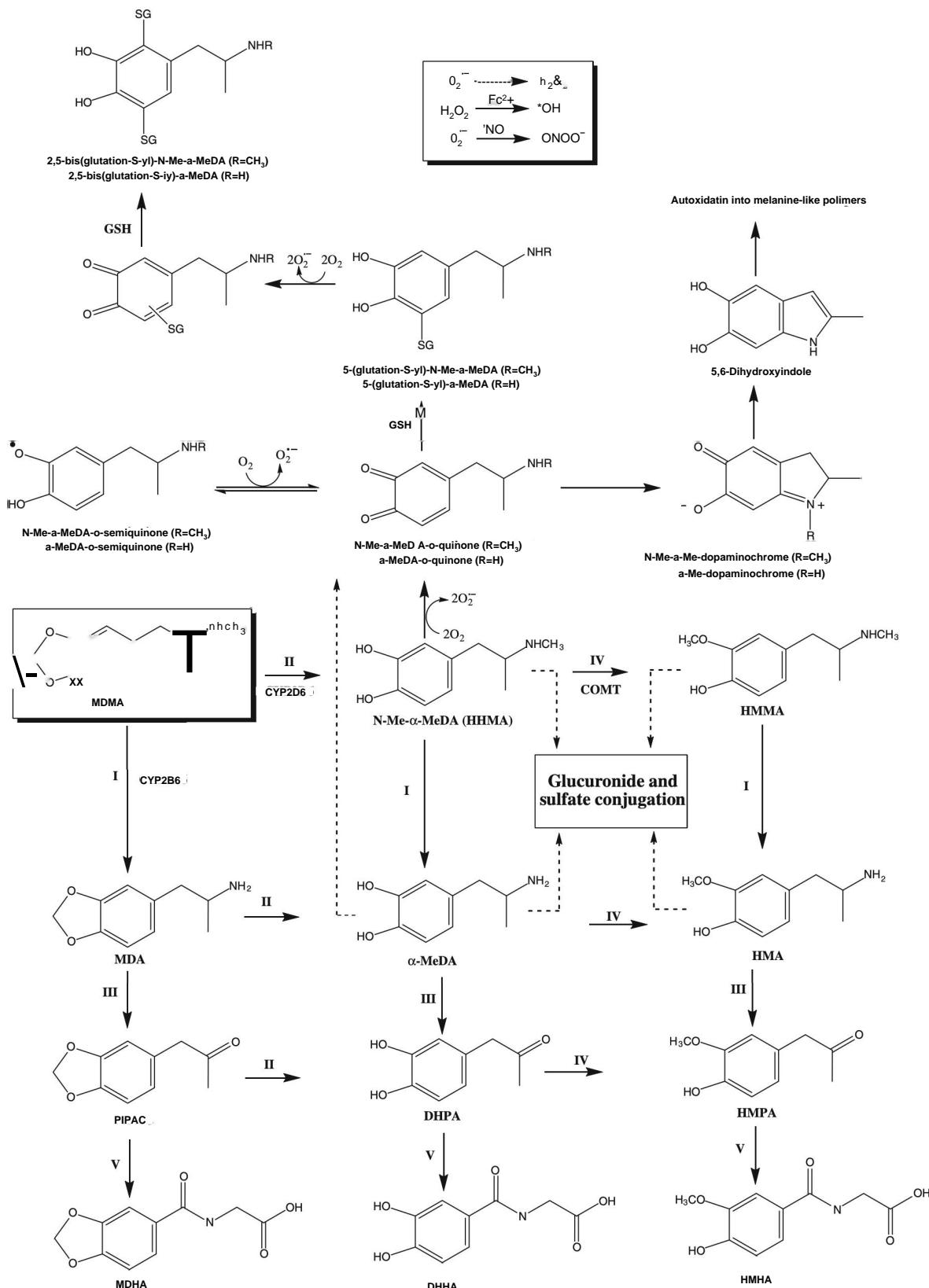


Fig. 5 MDMA metabolic pathways. I N-demethylation; II demethylenation; III oxidative deamination; IV O-methylation; V glycine conjugation; MDMA, 3,4-methylenedioxymethamphetamine; MDA, 3,4-methylenedioxymphetamine; N-Me-a-MeDA or HHMA, N-methyl-a-methyldopamine or dihydroxymethamphetamine; a-MeDA, a-methyldopamine; HMMA, hydroxymethoxymethamphetamine; HMA, hydroxymethoxyamphetamine; PIPAC, piperonylacetone; MDHA, 3,4-methylenedioxymhippuric acid; DHPA, 3,4-dihydroxyphenylacetone; DHHA, 3,4-dihydroxyhippuric acid; HMPA, 4-hydroxy-3-methoxypheylacetone; HMHA, 4-hydroxy-3-methoxyhippuric acid

Around 80% of MDMA is eliminated after hepatic metabolism, while approximately 20% of the dose is excreted unchanged in urine (de la Torre et al. 2004a). MDMA urinary elimination seems to be constant for different doses (around 60% urinary recovery, independently of the administered dose) (de la Torre et al. 2004a), while non-renal elimination is dose-dependent (de la Torre et al. 2000a). After the oral administration of a 75 mg dose, a 74.0 ± 71.1 L/h non-renal elimination rate was observed. However, after a 125 mg dose, this rate was 38.1 ± 13.3 L/h (de la Torre et al. 2000a) (see Table 3). As previously mentioned, this strongly suggests hepatic metabolism impairment at elevated MDMA doses. At high concentrations, MDMA competitively inhibits CYP2D6 in human liver microsomes (Wu et al. 1997). This inhibition occurs through the formation of a complex with the enzyme (Heydari et al. 2004). The formation of such complexes involves the carbene formation after the oxidation of substrates containing tertiary amines or a methylenedioxy group, both of which are present in MDMA molecular structure (Delaforge et al. 1999). This inhibition can occur within a period of 1 h after MDMA ingestion (at the doses commonly used for recreational purposes), and basal enzyme activity levels may only be restored after a period of at least 10 days (Yang et al. 2006).

O-methylated N-Me-a-MeDA, 4-hydroxy-3-methoxymethamphetamine (HMMA), is the main MDMA metabolite excreted in urine (over 20% of the dose) followed by the catechol metabolite N-Me-a-MeDA (Segura et al. 2001). These metabolites are mainly excreted as the glucuronide and sulfate conjugates (Helmlin et al. 1996). MDA urinary excretion represents less than 10% of the MDMA-ingested dose (Mas et al. 1999; Mueller et al. 2009). MDMA can also be excreted in feces, sweat, saliva, vitreous humor, hair, and nails. These biological samples may serve as alternatives to urine and blood for the detection of MDMA at relatively high concentrations (de la Torre et al. 2004a; Samyn et al. 2002). MDMA elimination is stereoselective, and the pharmacologically more active S-(±)-MDMA enantiomer is more rapidly metabolized and excreted than the R-(—)-MDMA enantiomer (Fallon et al. 1999; Meyer et al. 2002a; Moore et al. 1996; Ramcharan et al. 1998).

General mechanisms of amphetamines toxicity

Hyperthermia

Hyperthermia is considered to be one of the most life-threatening acute physiological consequences of the amphetamines intoxications. Case reports appear to indicate that the incidence and severity of hyperthermia vary among drugs, being the amphetamine derivatives most often implicated METH, MDMA, 3,4-methylenedioxymethamphetamine (MDEA, “eve”), and p-methoxyamphetamine (PMA) (Green et al. 2004; Jaehne et al. 2007). The most reported and best studied amphetamine, concerning its hyperthermic effects, is MDMA, for which body temperatures as high as 43 °C, have been reported in human users (Green et al. 2003; Henry et al. 1992). Noteworthy, hyperthermia mediated by these drugs seems to be responsible for frequent fatal complications that are also characteristic of heatstroke, such as rhabdomyolysis, acute renal failure, disseminated intravascular coagulation (DIC), multiple organ failure, and acidosis (Henry et al. 1992; Kalant 2001; Kendrick et al. 1977). To worsen this scenario, it is unlikely that any single pharmaceutical agent will be completely effective in reversing the hyperthermia (dantrolene may have some effectiveness—see below), so careful body cooling using cold baths or ice packs remains the principal clinical approach.

Body temperature regulation is complex and requires a balance between heat production and dissipation. In terms of heat production, all stimulant drugs increase CNS metabolic activity and therefore potentially induce hyperthermia (Parrott 2012; Rusyniak and Sprague 2005). The other side of thermal homeostasis is heat dissipation. In animals, this involves increasing the blood supply to the tail in rats, ears in rabbits, and piloerection in all hairy mammals to facilitate heat loss. In humans, the main physiological route is peripheral vasodilatation, with more warm blood to the skin, increased skin temperature, and heightened sweating to facilitate heat loss (Parrott 2012).

As already noted, the most studied amphetamine concerning the mechanisms leading to hyperthermia is MDMA. For that reason, only MDMA-related studies will be analyzed in the present section. The effect of MDMA on body temperature is complex because the drug has actions on all major monoamine neurotransmitters [5-HT, DA, and noradrenaline (NA)] both by releasing the amines from nerve endings and also by acting on their receptors. These neurotransmitters interact in complex ways to control temperature with actions involving both central thermoregulation and peripheral changes in blood flow and brown adipose tissue thermogenesis (Docherty and Green 2010). There is now considerable evidence suggesting that 5-HT plays little or no direct role in the acute hyperthermic

Table 7 Pharmacokinetic parameters of MDMA metabolites in humans

Metabolite	MDMA dose (mg)	n	Isomer studied	Cmax (μg/L)	t _{max} (h)	AUC ₀₋₂₄ (pg·h/L)	t _{1/2} (h)	Ae (%)	Reference
MDA	50	1		28.4	4			7	Verebey et al. (1988)
MDA	50	1		5.1	6	51.1	5.6	0.54	de la Torre et al. (2000a, b)
HMMA		2						34.4–58.7	
HMA		2						1.6–1.8	
MDA	75	8		7.8 ± 2.5	5.1 ± 2.6	122.3 ± 66.7	16.1 ± 18.3	0.9 ± 0.2	de la Torre et al. (2000a, b)
HMMA		8						33.1 ± 5.6	
HMA		8						1.4 ± 0.1	
MDA	100	2		22.4–14.2	6–4	345.4–61.5	6.3–6.4	0.27–1.1	de la Torre et al. (2000a, b)
HMMA								11.5–23.9	
HMA								0.6–1.3	
MDA	100	8		13.1 ± 4.5	6.7 ± 2.6		24.9 ± 14.5	1.5 ± 0.6	de la Torre et al. (2004b)
HHMA		8		154.5 ± 76.6	1.2 ± 0.3		13.4 ± 8.1	17.7 ± 4.6	
HMMA		8		236.7 ± 87.1	2.3 ± 0.9		11.2 ± 2.9	22.7 ± 7.7	
HMA		8		7.5 ± 4.0	8.2 ± 1.7		37.4 ± 17.9	1.35 ± 0.3	
MDA	125	8		13.7 ± 1.6	7.1 ± 2.8	215.2 ± 68.5	27.7 ± 26.0	0.99 ± 0.4	de la Torre et al. (2000a, b)
HMMA								22.9 ± 15.9	
HMA								0.96 ± 0.6	
MDA	150	2		34.2–31.4	4–10	590.0–373.9	37.3–23.2	0.3–0.6	de la Torre et al. (2000a, b)
HMMA								15.7–10.6	
HMA								0.53–0.48	
HHMA	1.6 (mg/kg)	9		151.8 ± 33.5	1.6 ± 0.5	1,801.2 ± 390.5	11.9 ± 2.8		Mueller et al. (2009)
HMMA				167.7 ± 41.6	1.7 ± 0.4	2,060.2 ± 327.5	13.7 ± 4.0		
MDA	1.5 (mg/kg)	2		15	6.3				Helmlin et al. (1996)
HMMA	100	4		307.1 ± 85.5	2.0 ± 0.0	3,190.9 ± 714.5	8.3 ± 1.3	22.7	Segura et al. (2001)
HHMA	100	4		154.5 ± 76.6	1.2 ± 0.3	1,990.94 ± 647.1	13.4 ± 8.1	17.7	
MDA	40	8	(R)	1.0 ± 0.3				1.0 ± 0.3	Fallon et al. (1999)
			(S)	3.0 ± 1.1				1.4 ± 0.5	
MDA	100	7	Racemate	13.0 ± 2.3	6.6 ± 1.9	308.4 ± 73.1 ^a	17.7 ± 6.2		Pizarro et al. (2004)
HMMA	100	7	Racemate	163.8 ± 71.4	2.8 ± 0.8	2,293.2 ± 881.5 ^a	10.4 ± 2.4		
			(R)	65.5 ± 26.1	2.9 ± 0.7	868.9 ± 453.3 ^a	13.5 ± 4.1		
			(S)	62.1 ± 21.6	2.6 ± 0.6	585.3 ± 216.6 ^a	5.9 ± 1.0		
HHMA	100	7	(R)	38.9 ± 12.4	2.4 ± 1.9	653.5 ± 22.2 ^a	42.6 ± 56.3		
			(S)	90.9 ± 38.8	2.3 ± 1.8	999.2 ± 459.0 ^a	7.9 ± 2.7		
HMMA	1.0 (mg/kg)	17		171.9 ± 79.5	1.8 ± 0.7	1,839.2 ± 502.9 ^b	11.5 ± 5.5		Fowler et al. (2008)
MDA		17		8.4 ± 2.1	7.5 ± 1.7	1,882.2 ± 54.4 ^b	10.6 ± 4.3		
HMA		13		3.5 ± 0.4	10.6 ± 2.6	63.2 ± 40.9 ^b	63.2 ± 40.9		

Table 7 continued

Metabolite	MDMA dose (mg)	n	Isomer studied	C_{max} ($\mu\text{g}/\text{L}$)	t_{max} (h)	AUC_{24} ($\mu\text{g}^*\text{h}/\text{L}$)	$T_{1/2}$ (h)	Ae (%)	Reference
HMMMA	1.6 (mg/kg)	17		178.0 ± 9.8	1.9 ± 0.7	8874.4 ± 970.1 ^b	18.4 ± 2.7		
MDA		17		18.8 ± 8.8	0.0 ± 0.0	87 ± 8 ± 111.8 ^a	12.8 ± 8.7		
HMA		16		8.9 ± 0.9	1.1 ± 0.9	122.0 ± 17.7 ^a	122.8 ± 17.7		

^a AUC from 0 to 48 h after MDMA administration^b AUC from 0 to ∞

C_{max} maximum plasma concentration, t_{max} time to maximum plasma concentration, AUC_{24} area under the plasma concentration–time curve from 0 to 24 h after administration, $T_{1/2}$ elimination half-life; Ae (%) amount excreted in 24-h urine collection expressed as % of ingested dose

response, due to the relative inefficacy of selective and non-selective 5-HT receptor antagonists and 5-HT uptake inhibitors to modulate MDMA-induced hyperthermia (Docherty and Green 2010). Nevertheless, the initial release of 5-HT also upregulates DA biosynthesis and release by activation of 5-HT2A post-synaptic receptors, which, through subsequent activation of D1 receptors, leads to the hyperthermic response (Mills et al. 2004).

Several studies have revealed a complex interaction between the hypothalamic-pituitary-thyroid (HPT) axis, sympathetic nervous system, and the activity of uncoupling proteins (UCP). Hypophysectomized and thyroparathyroidectomized rats treated with the same dose of MDMA did not become hyperthermic and in fact displayed a significant hypothermia. When thyroid hormone was replaced to thyroparathyroidectomized rats, they experienced the hyperthermic response, arguing for a role of the HPT on the hyperthermic effects of MDMA (Sprague et al. 2003). Thermoregulation within the hypothalamus has been suggested to be controlled by 5-HT, DA, and NA, and, as reviewed by Rusyniak and Sprague (2005), MDMA activates the HPT axis, with subsequent thermogenesis and toxicity being dependent on the circulating levels of thyroid and adrenal hormones. When activated neurons in the anterior hypothalamus stimulate the sympathetic nervous system, NA is released from nerve endings into the circulatory system. Acting through vascular α1-adrenoreceptors, NA induces vasoconstriction and impairs heat dissipation. In concert with the thyroid hormones, norepinephrine also binds to and activates α1- and β 3-adrenoreceptors, regulating the activity of thermogenic tissues, such as brown fat and muscle, through UCP (Rusyniak and Sprague 2005). Incorporation of UCPs in mitochondria, referred to as mitochondrial uncoupling, dissociates the mitochondrial proton gradient from ATP synthesis and releases the free energy as heat (Mills et al. 2004). Three heat uncoupling proteins are currently known: UCP-1 in brown fat of rodents, UCP-2 in the liver, and UCP-3 in human skeletal muscles. The activation of the skeletal muscle thermogenic protein, UCP-3, was demonstrated to have an important role in MDMA-induced hyperthermia. In fact, mice deficient in a mitochondrial protein, known as UCP-3 (UCP3-/-), have a diminished thermogenic response to MDMA and therefore are protected against its toxic effect (Mills et al. 2003).

As mentioned above, peripherally, the increased body temperature seen with MDMA is also due to vasoconstriction. Hyperthermia activates sympathetic vasodilator activity increasing cutaneous blood flow and subsequently increasing convective heat transfer from the core to the periphery (Mills et al. 2004). MDMA induces cutaneous vasoconstriction, and this cutaneous restriction in blood

flow contributes to the increase in core body temperature (Pedersen and Blessing 2001).

MDMA was also shown to produce aggregate toxicity in mice, an event related to MDMA-induced hyperthermia (Capela et al. 2009). The term aggregate toxicity refers to the finding that the toxicity and lethality of MDMA increases in injected animals housed in groups compared to those housed singly. MDMA-aggregate toxicity is closely related to its hyperthermic effects, especially in crowded settings. Given that MDMA is usually consumed in the context of crowded, hot environment (such as what commonly occurs at rave parties) and prolonged physical exertion, these factors may also strongly contribute to the hyperthermic effect that occurs in humans (Freedman et al. 2005; Patel et al. 2005).

In experimental laboratory animals, there are reports confirming that ambient temperatures can influence the effect of MDMA and other amphetamines on body temperature, as MDMA-treated animals exposed to low environmental temperature (below 22°C) tend to develop hypothermia, whereas under high environmental temperature (above 28°C) can reach life-threatening hyperthermia (Capela et al. 2009). Overall, when evaluating the thermo-regulatory effects of MDMA, one must take into account the environmental temperature at which the experiment is conducted. Along with elevated ambient temperature, motor activity increases the toxicity of stimulants such as AMPH and MDMA. Because motor activity can increase body temperature and exhaust supplies of ATP, it is not surprising that the combination of increased motor activity and stimulant use results in exaggerated toxicity (Rusyniak and Sprague 2005).

There is marked similarity between clinical signs and symptoms of MDMA intoxication and a malignant hyperthermia crisis, though the heat-generation mechanisms at the muscle level are quite different. Malignant hyperthermia is an autosomal-dominant inherited disorder of the skeletal muscle cell, characterized by a hypermetabolic response to halogenated volatile anesthetics and depolarizing muscle relaxants. It involves disruption of intracellular calcium homeostasis caused by a defect in the ryanodine receptor type 1 (Wappler 2001). On the other hand, the pathophysiological mechanism of MDMA intoxication at the skeletal muscle level is most likely to be the combination of its agonistic effect on the nAChR of the skeletal muscle, the increased sensitivity of the contractile apparatus to Ca^{2+} , and the cytotoxicity of MDMA metabolites (Gerbershagen et al. 2012). In spite of the mechanistic differences, the similar disruption of Ca^{2+} homeostasis explains why dantrolene, a drug used in the treatment of malignant hyperthermia through inhibition of Ca^{2+} release, is currently recommended for MDMA-induced hyperpyrexia by several poison control centers. Though the effectiveness of this drug is still

controversial, it may lower mortality rates and reduce the incidence of severe complications, especially in patients with severe ($\geq 40^\circ\text{C}$) or extreme ($\geq 42^\circ\text{C}$) hyperpyrexia (Grunau et al. 2010).

Oxidative stress

Formation of ROS and/or RNS

The formation of ROS and/or RNS and the resulting oxidative and/or nitrosative stress is a common toxicological pathway of amphetamines, which has an important role on the observed pathogenesis, both at peripheral organs (Carvalho et al. 2010; Ninkovic et al. 2008; Shenouda et al. 2010) and the CNS (Alves et al. 2009; Cadet et al. 1994; Capela et al. 2007b). In the present section, the mechanisms involved in the formation of ROS and RNS will be briefly explained.

Oxidative deamination of monoaminergic neurotransmitters by monoamine oxidase

One of the most important pathways leading to sustained production of ROS mediated by amphetamines is related to their general pharmacological mechanism of action: the massive release of monoamine neurotransmitters (mainly 5-HT, DA, and NA) from neuronal storage vesicles. While still inside the neuronal cytoplasm, part of these monoamines will undergo oxidative deamination by MAO, present in the external membranes of mitochondria (Alves et al. 2009; Cadet et al. 1994; Capela et al. 2007b). This metabolic transformation produces H_2O_2 , as a by-product. H_2O_2 then interacts with transition metal ions such as iron (Krasnova and Cadet 2009; Quinton and Yamamoto 2006), to form toxic hydroxyl radicals (Nagatsu 2004). Using mouse brain synaptosomes as experimental model, it was demonstrated that H_2O_2 generation induced by incubation of synaptosomes with DA and 5-HT was MAO-dependent (Barbosa et al. 2012). 5-HT has been shown to be metabolized in vitro by MAO-A ($K_m = 178 \pm 2 \text{ pM}$) and MAO-B ($K_m = 1,170 \pm 432 \text{ pM}$), which means that metabolism by MAO-B is only residual in the presence of MAO-A (Shih et al. 1999). It is important, nevertheless, to mention that MAO-B is fully effective in the absence of MAO-A, as it happens inside serotonergic nerves (Alves et al. 2009; Alves et al. 2007).

Metabolism of amphetamines containing a methylenedioxy group and auto-oxidation of catecholamines

Hepatic metabolism of amphetamines containing a methylenedioxy group is a significant source of ROS and other chemically reactive compounds. MDMA is the best-known

example, but this methylenedioxy group is also present in MDA, methylone, butylone, among others. As discussed before, the hepatic metabolism of MDMA involves N-demethylation to MDA. MDMA and MDA are O-demethylenated to N-Me-a-MeDA and a-MeDA, respectively (Kumagai et al. 1991; Lim and Foltz 1998; Pizarro et al. 2004). These metabolites, formed in liver cells, can reach the heart, the kidney, the brain, and other organs via the circulation and produce their toxic effects, mainly due to the auto-oxidation of the catecholic groups into reactive o-quinones (Macedo et al. 2007; Spencer et al. 1998). Another source of this group of reactive compounds are catecholic neurotransmitters and respective precursors or metabolites, especially DA, L-Dopa, and 3,4-dihydroxyphenylacetic acid (DOPAC), which also undergo non-enzymatic, spontaneous auto-oxidation to the corresponding o-quinones (Fiaschi and Cerretani 2010). Apart from auto-oxidation, o-quinones are also generated by the enzymatic oxidation of DA by prostaglandin H synthase (cyclooxygenase: COX), lipoxygenase, tyrosinase, and xanthine oxidase (Kita et al. 2009). These quinones may be oxidized to the cyclized aminochromes and are then finally polymerized to form melanin, but may otherwise exert toxicity to nerve endings. As recently reviewed (Kita et al. 2009; Krasnova and Cadet 2009; Song et al. 2010), quinones are highly redox-active molecules that can undergo the following pathways: (1) a redox cycle producing semiquinone radicals, leading to the generation of superoxide radicals and H_2O_2 . Subsequent formation of hydroxyl radicals (HO^-) through interactions of superoxide and hydrogen peroxide with transition metals leads to oxidative stress, mitochondrial dysfunctions, and peroxidative damage to pre-synaptic membranes; (2) irreversible 1,4-intramolecular cyclization with subsequent formation of aminochromes; (3) conjugation with GSH to form a glutathionyl adduct that can further react with GSH and protein thiols, leading to GSH depletion and formation of protein adducts, leading to inactivation of the target proteins. In particular, it is of interest that DA quinones generated in the brain covalently modify and inactivate tyrosine hydroxylase and the DA transporter, subsequently inhibiting both DA synthesis and uptake.

Generation of ROS in mitochondria

ROS are inevitable products of the normal respiration in mitochondria. Studies on isolated mitochondria have identified complex I and complex III as possible sites of ROS generation in the electron respiratory chain (ETC) (Votyakova and Reynolds 2001). Thus, compounds that interfere with these mitochondrial complexes may lead to increased ROS production. The first investigation of METH- and MDMA-induced alterations in the function of

specific ETC complexes showed that both METH and MDMA decrease levels of cytochrome oxidase, a marker of ETC complex IV activity (Burrows et al. 2000). In subsequent studies, a decrease in complex II–III but not I–II activity was observed in the striatum at both 1 and 24 h after METH (Brown et al. 2005). More recently, it was demonstrated that the exposure of an adolescence rat model to a neurotoxic binge administration of MDMA (four times, 10 mg/kg, i.p., every 2 h) induced oxidative stress to whole-brain mitochondria (Alves et al. 2007). Additionally, analysis of mitochondrial DNA (mtDNA) revealed that ND_I (nicotinamide adenine dinucleotide phosphate dehydrogenase subunit I) and ND_{II} (nicotinamide adenine dinucleotide phosphate dehydrogenase subunit II) subunits of mitochondrial complex I and cytochrome c oxidase subunit I of complex IV suffered deletions in MDMA-exposed animals. Inhibition of MAO-B by selegiline did not reduce hyperthermia, but reversed MDMA-induced effects in the oxidative stress markers, mtDNA, and related protein expression (Alves et al. 2007). Since MAO is localized in the outer membrane of the mitochondria, the formation of H_2O_2 resulting from the enzyme metabolism of MDMA-released monoamine neurotransmitters (mostly NA, 5-HT, and DA) will mostly affect the mitochondria itself. As explained below, another effect mediated by amphetamines is the rise in intracellular Ca^{2+} due to the excitotoxic effect of glutamate. This effect may also lead to inhibition of mitochondrial function with consequent increased ROS production (Brown et al. 2005).

Oxidative damage to the mitochondria due to overproduction of ROS can initiate the intracellular cascade of reactions leading to neurotoxicity. In particular, METH has been shown to induce increases in proapoptotic proteins, BAX and BID, and decreases in antiapoptotic proteins, Bcl-2 and Bcl-XL, which results in the activation of downstream apoptotic cascade, characterized by release of mitochondrial proteins cytochrome c, apoptosis-inducing factor (AIF), and Smac/DIABLO into the cytosol followed by activation of caspases 9 and 3, and the breakdown of several structural cellular proteins (Cadet and Krasnova 2009).

Excitotoxicity and production of RNS

Excessive glutamate release induced by amphetamines has been linked with NO-mediated nitration of proteins in DA and 5-HT terminals and neuronal cell death (Krasnova and Cadet 2009; Quinton and Yamamoto 2006; Yamamoto and Raudensky 2008). This process, termed excitotoxicity, is mediated by the activation of ionotropic and group 1 metabotropic glutamate receptors (iGluR and mGluR, respectively), leading to a rise in intracellular Ca^{2+} levels. This rise in Ca^{2+} leads to activation of a variety of calcium-dependent enzymes, namely NO synthase, with

subsequent generation of NO and ensuing RNS, as well as activation of apoptotic pathways, culminating in failure of cellular organelles, such as mitochondria and endoplasmic reticulum (ER), breakdown of cytoskeletal proteins, and DNA damage (Yamamoto et al. 2010). An increase in NO and ONOO⁻-mediated nitration of proteins is important in light of the fact that tyrosine hydroxylase and tryptophan hydroxylase, biosynthetic enzymes of DA and 5HT, respectively, are readily nitrated by both NO and ONOO⁻ (Fiaschi and Cerretani 2010). Additionally, ONOO⁻ is known to decrease mitochondrial complex II-III activity (Yamamoto and Raudensky 2008). Among the enzymes activated by glutamate in the event of stimulation by amphetamines is the protease calpain I leading to the proteolysis of several cytoskeletal proteins such as spectrin, tau, and microtubule-associated protein 2 (MAP 2) (Quinton and Yamamoto 2006). Another downstream effect of calpain activation may occur in relation to METH- and MDMA-induced increases in oxidative stress. Glutamate-mediated calpain activation also catalyzes the conversion of xanthine dehydrogenase to xanthine oxidase, which catabolizes xanthine and hypoxanthine to uric acid, yielding superoxide radicals in the process (Dykens et al. 1987).

Microglial activation

Microglia are the resident immune cells within CNS that function to protect the brain against injury or damage. Although microglial activation is necessary for host defense and neuron survival, the overactivation of microglia results in deleterious and neurotoxic consequences. Amphetamines, like METH, MDMA, AMPH, and p-chloroamphetamine, induce a substantial microglial response in the areas of the brain that show neuronal degeneration, mediating the release of toxic substances such as superoxide radicals, NO, pro-inflammatory cytokines, and prostaglandins, which have already been implicated in their neurotoxicity (Cadet and Krasnova 2009; Thomas et al. 2004). Another mechanism by which microglial activation by amphetamines may contribute to neurotoxicity is via increases in the expression of cytokines such as IL-1/1, IL-6, and TNF-a, which initiate and promote neuroinflammation (Yamamoto and Raudensky 2008).

Depletion of antioxidants

Amphetamines can also cause oxidative stress by decreasing the activity or expression of antioxidant enzymatic and/or non-enzymatic antioxidant systems, including Cu-Zn superoxide dismutase (SOD), catalase, GSH, glutathione peroxidase (GPX), glutathione reductase (GR), glutathione S-transferase (GST) and peroxiredoxins (Cadet

and Krasnova 2009; Carvalho et al. 1996, 2002a, 2004b). The depletion of these crucial endogenous antioxidants may render the affected cells defenseless against the deleterious effects of ROS and RNS.

Hyperthermia

One of the mechanisms by which amphetamines increase the formation of ROS and RNS is through hyperthermia. In fact, free radical formation is inhibited when the acute MDMA-induced hyperthermia is prevented (Colado et al. 1999). Furthermore, prevention of MDMA-induced hyperthermia decreases the neurotoxicity, and many drugs that protect against MDMA-induced neurotoxicity also decrease body temperature (Fiaschi and Cerretani 2010). Though the pathways leading to the higher production of ROS and RNS under hyperthermic conditions remain elusive, mitochondria, one of the main sources of ROS in cells, undergo a temperature-dependent uncoupling during increases in temperature, associated with increased superoxide formation (Brown et al. 2005; Flanagan et al. 1998). Hyperthermia also increases the conversion of the enzyme xanthine dehydrogenase to the oxidase form, an important source of oxygen-derived free radicals (Skibba et al. 1989).

Amphetamines Neurotoxicity

One of the most feared and debated health risks of amphetamines is related to their potential neurotoxic effects. Indeed, this subject has been extensively researched in the past 4 decades. When typing in the USA governmental website "PubMed" the combination "amphetamine and neurotoxicity," one can find more than a thousand papers on the subject. Using the same strategy, the combination "methamphetamine and neurotoxicity" will provide more than 600 papers, and for "3, 4-methylenedioxymethamphetamine and neurotoxicity" more than 450 papers are listed. Despite this huge amount of research, there are still many unsolved issues that warrant further research. In this chapter, findings of laboratory studies in animals and available data on the neurotoxicity of amphetamines in humans will be discussed.

Amphetamines promote the release of monoamines in the brain

Amphetamines act as substrate-type releasers. They bind to the plasma membrane monoamine transporters, being transported and translocated into the cytoplasm, stimulating neurotransmitter release through these transporters (Kahlig et al. 2005; Ramamoorthy and Blakely 1999; Rothman et al. 2001; Sulzer et al. 1995). Amphetamines

present different affinities toward the monoamine transporters, DAT, NET, and 5-HTT. Nevertheless, the interaction with these transporters is essential to trigger the release of monoamines, since in their absence, or inhibition, amphetamines do not elicit their biological effects (Sitte and Freissmuth 2010). Amphetamines induce NA, DA, and 5-HT neurotransmitter release by two mechanisms: (1) neurotransmitters exit the cell along their concentration gradients via reversal of normal 5-HTT function and (2) cytoplasmic concentrations of transmitters are increased due to drug-induced disruption of vesicular storage (Azmitia et al. 1990; Berger et al. 1992; Crespi et al. 1997; Gudelsky and Nash 1996; Partilla et al. 2006; Wichems et al. 1995). In a first step, amphetamines are recognized by DAT, NET, and/or 5-HTT and enter the monoaminergic neuron. Inside the cell, amphetamine molecules will be preferentially in their protonated form, because the intracellular pH is lower than the extracellular pH. Unprotonated amphetamine molecules can diffuse back into the synaptic cleft through the membrane and be quickly available for another round of transporter-mediated uptake (Sitte and Freissmuth 2010). Once in the cytoplasm, the rapid enhancement of monoamine release from the storage vesicles by amphetamines occurs via a carrier-mediated exchange mechanism. Amphetamines are substrates for vesicular monoamine transporter (VMAT) and possibly enter the vesicles via VMAT and deplete vesicular neurotransmitter storage by reversal of transporter activity (Partilla et al. 2006). Amphetamines can also deplete vesicular biogenic amine content by disrupting the pH gradient, via a weak base effect that powers the transporter (Fleckenstein and Hanson 2003). Moreover, amphetamines are known for their MAO inhibitory properties, therefore increasing the cytosolic content of monoamines through inhibition of their metabolism (Mantle et al. 1976). These coordinated actions explain why amphetamines are potent monoamine releasers.

Another important aspect of the brain actions of amphetamines is their ability to regulate the activity of the monoamine transporters. Amphetamines are known to regulate the phosphorylation state of the transporter, thereby regulating their function (Cervinski et al. 2005; Ramamoorthy and Blakely 1999). The loss of the transporter function is accompanied by the loss of surface-expressed transporters. Overall, the modulation of transporter activity and sequestration seems to be a feature of all monoamine transporter substrates.

When relating these actions with neurotoxicity, it is important to notice that an increase in the cytoplasmic pool of monoamines triggers oxidative stress inside the nerve terminal by two mechanisms. First, the auto-oxidation properties of catecolamines, DA, and NE can produce deleterious ROS. Second, the metabolism of monoamines

by the active MAO isoforms can also lead to ROS as by-products. Through these coordinated actions, the toxicity inside the monoaminergic terminal is increased and nerve terminal loss can occur (Capela et al. 2009).

Initial reports on the neurotoxicity of amphetamines: observational studies

The brain neurotoxic actions of amphetamines have been evaluated mainly through biochemical and histological or immunocytochemical techniques. The biochemical markers of neurotoxicity include the decreased levels of monoamines and their major metabolites, the decrease in the monoamine transporter binding sites, as well as the lower expression and/or activity of enzymes involved in the synthesis and metabolism of brain monoamine neurotransmitters. The histological or immunocytochemical indicators of neurotoxicity use staining methods to mark monoaminergic neurons. This can be achieved by using silver staining methods or specific antibodies directed toward specific neuronal markers. The fact that neuronal markers are depleted after amphetamines administration does not necessarily imply that neurodegeneration has indeed occurred. Absolute direct identification of neurotoxic damage can only be made with histological or immunocytochemical techniques that can reveal neurodegeneration. Neurodegeneration can be partial, with the loss of neuronal terminals, axons, or dendrites, or total with total neuron loss.

Probably, the first published paper that clearly described that AMPH could produce depletion of the monoamine content was published in 1961. McLean and McCartney found that rats treated with S-(+)-amphetamine enantiomer (d-AMPH) sulfate presented lowered brain NA levels, an effect that the authors reported to last for several days after treatment (McLean and McCartney 1961). In 1962, another paper confirmed this event in rabbits, which presented lower NA levels in the hypothalamus, after a single s.c. injection of 20 mg/kg of d-AMPH sulfate (Sanan and Vogt 1962). In 1963, another paper reported that mice had lower NA brain levels 4 h after AMPH administration. Moreover, the depletion increased in a dose-dependent manner (Moore 1963). Years later, two papers published in *Science* reported that AMPH promoted selective damage to dopaminergic neurons in the rat brain, accompanied by DA depletion and decreased tyrosine hydroxylase (TH) activity, which lasted several days after AMPH administration (Ellison et al. 1978; Fuller and Hemrick-Luecke 1980).

Other amphetamines were, as well, reported to deplete brain monoamine levels. Chloroamphetamines, namely p-chloroamphetamine, were shown to produce brain depletions of 5-HT, both in rats and guinea pigs (Pletscher et al. 1964; Sanders-Bush and Sulser 1970). Methamphetamine

and fenfluramine administration to rats also caused depletion of brain monoamines. In rats, METH (90 pmol/kg, i.p.) caused depletion of brain NA and 5-HT, whereas fenfluramine (90 pmol/kg i.p.) produced a selective and long-lasting depletion of brain 5-HT (Morgan et al. 1972).

The neurotoxic actions of amphetamines are not limited to depletions of monoamine brain levels. Actual degeneration of neuronal fibers has been shown in the brain of laboratory animals. Pellets containing d-AMPH implanted subcutaneously in rats, which released this drug continuously for 10 days, promoted swollen DA axons in the caudate nucleus (Ellison et al. 1978). Also in the mouse model, infusion of large doses of d-AMPH continuously for 7 days by means of osmotic minipumps caused a long-lasting reduction of DA nerve terminals, which was demonstrated histochemically in the striatum of mice (Jonsson and Nwanze 1982). It was found that METH induces terminal degeneration along with correlative DA neurochemical deficits in the neostriatum and nucleus accumbens of rats (Ricaurte et al. 1982). Rats treated with METH (15 mg/kg, s.c.) every 6 h for 24 h, and killed 6 and 11 days after treatment, presented a significantly increased number of swollen nerve DA fibers in the neostriatum (Hanspeter 1981). Also in rats, METH and AMPH continuously administered for 3 days by means of subcutaneously implanted osmotic minipumps (total dose of each drug was approximately 4 mg/day) presented selective striatal DA depletion accompanied by striatal nerve fiber degeneration (Ricaurte et al. 1984).

Another amphetamine, MDMA, was also reported to promote neurotoxic actions toward the CNS. Most likely, the first report proving that MDMA induces neurotoxicity was conducted in rats and was published in 1986 (Schmidt et al. 1986). In the following year, there were already, at least, six papers corroborating MDMA-induced serotonergic neurotoxicity to rats (Battaglia et al. 1987; Commins et al. 1987; Schmidt 1987; Schmidt et al. 1987; Stone et al. 1987a, b). Nonetheless, in 1985, one year before the first report on MDMA-induced neurotoxicity, another study published in *Science* had reported that MDA, a major active metabolite of MDMA, produced serotonergic neurotoxicity (Ricaurte et al. 1985). MDMA was shown to promote damage to the terminal portions of axons, as indicated by the reduced density of fine, arborized 5-HT axons and sparing of smooth, straight pre-terminal fibers, while fibers of passage and raphe cell bodies were unaffected (Molliver et al. 1990; O'Heam et al. 1988). In rats, 2 weeks after systemic administration of MDA or MDMA (20 mg/kg, s.c., twice daily for 4 days), a selective and profound loss of 5-HT axons throughout the forebrain, and fragmented 5-HT axons anatomic evidence for degeneration of 5-HT projections, was observed (O'Heam et al. 1988). Moreover, the loss of the 5-HT terminals in rats is

both biochemically and histologically comparable to the one that occurs following exposure to a classic 5-HT neurotoxin, 5,7-dihydroxytryptamine (Capela et al. 2008; Xie et al. 2006).

In non-human primates, the neurotoxic actions of amphetamines were also studied and reported. Long-lasting depletion of DA and other DA nerve terminal markers has been reported in striatum of non-human primates receiving METH. Rhesus monkeys were treated for 3–6 months with i.v. injections of METH 8 times/day (final dose 3.0–6.5 mg/kg/injection) (Seiden et al. 1976). After this regimen, monkeys exhibited fairly uniform depletion of NA in all brain areas 24 h after the last injection, and NA levels remained low in the midbrain and frontal cortex, but returned to normal levels in the pons-medulla and hypothalamus. Most importantly, this regimen also caused a 70–80% reduction of caudate DA levels in monkeys treated over 3–6 months (Seiden et al. 1976). Also in rhesus monkeys, METH administered s.c. over a 2-week period promoted decreases in DA and 5-HT, but not NA levels, in various brain regions. Noteworthy, the decrease in caudate DA levels was accompanied by a decrease in the number of DA uptake sites and a decrease in the cerebrospinal fluid concentration of homovanillic acid (HVA) (Preston et al. 1985). Another study, also conducted in rhesus monkeys, reported that approximately 4 years after the last drug injection, the levels of DA and 5-HT in caudate were below control levels as were concentrations of 5-HT in several other brain regions. The authors concluded that, although a possible partial recovery can occur, these results strongly suggested that METH-induced neurotoxicity may be permanent in the monkey brain (Woolverton et al. 1989).

MDMA-induced neurotoxicity was demonstrated in squirrel monkeys that presented reduced serotonergic innervation and reduced 5-HT levels, 7 years following exposure to the drug (Hatzidimitriou et al. 1999). This study clearly showed that the damage of MDMA toward the serotonergic system is long lasting and apparently irreversible. In another study conducted with squirrel monkeys, which were previously challenged with MDMA (total dose 40 mg/kg, s.c.), the authors reported substantial serotonergic axonal sprouting and a highly abnormal re-innervation pattern 18 months after MDMA (Fischer et al. 1995).

Following these reports on the neurotoxic actions of amphetamines, many others continued to prove that administration of single or multiple doses of amphetamines to mice, rats, or non-human primates results in neurotoxicity to dopaminergic or serotonergic neurons, but also to other types of neurons. Initial reports on the neurotoxic effects of amphetamines were mainly focused on the damage of serotonergic and dopaminergic systems.

Nonetheless, more recent studies demonstrate a broader neuronal cell death. MDMA produced neuronal degeneration in several rat brain areas such as the cortex, hippocampus, the ventromedial/ventrolateral thalamus, and the tenia tecta (Commins et al. 1987; Meyer et al. 2004; Schmued 2003; Warren et al. 2007). Methamphetamine administrated to mice was shown to cause neuronal death in several brain areas including the striatum, hippocampus, cortex, indusium griseum, medial habenular nucleus, and amygdala (Bowyer and Ali 2006; Deng et al. 2001; Jayanthi et al. 2004; Warren et al. 2007; Zhu et al. 2006). Therefore, the neurotoxicity of amphetamines is not only limited to the serotonergic and dopaminergic nerve terminals but also promotes actual neuronal death in the cortex, striatum, and hippocampus of laboratory animals (Krasnova et al. 2005). These results, obtained *in vivo*, were also demonstrated in cultured neurons. Methamphetamine, MDMA, and other amphetamines were proven to induce neuronal apoptosis in cultured rat cortical and cerebellar granule neurons (Capela et al. 2006a, b, 2007a; Jimenez et al. 2004; Stumm et al. 1999).

In summary, from the above-mentioned studies, it is possible to conclude that (1) amphetamines promote neurotoxic actions toward monoaminergic neurons in the brain of laboratory animals; (2) the neurotoxic actions are manifested by long-lasting depletions of brain neurotransmitters and their metabolites, reduction of monoamine transporter activity, and terminal neuronal damage; (3) AMPH and METH are usually more prone to promote damage to the dopaminergic system, while MDMA is regarded as serotonergic neurotoxins; and (4) despite terminal degeneration of monoaminergic neurons, other types of neurons can also be affected.

Neurotoxicity of amphetamines in experimental animals: neuroprotection studies

In order to reveal the mechanisms by which amphetamines promote neurotoxic actions, many studies were performed not only in animals but also in *in vitro* models. These studies have revealed several mechanisms by which amphetamines produce neurotoxic actions, though much is still to be discovered. Most importantly, the main goal is to find a therapeutic strategy that can be useful to prevent and/or treat the neurotoxic events induced by amphetamines.

When using laboratory animals, researchers generally find that amphetamines produce an elevation of body core temperature. This issue was neglected by many researchers in the earlier studies of neurotoxicity, but subsequent reports clearly related the hyperthermic effect to the neurotoxicity of amphetamines. Male rats treated with 5 mg/kg METH (4 doses, each 2 h apart) at an environmental temperature of 23°C presented striatal DA levels

down to 70% of controls 2 weeks after treatment (Bowyer et al. 1992). However, no changes in striatal DA levels were observed in rats given the same METH regimen at an environmental temperature of 4°C. Furthermore, striatal TH activity was not affected by 10 mg/kg METH at 4°C, but decreased to approximately 50% of control, 3 days after the same METH dose at 23°C. Thus, a cold environmental temperature could prevent the long-term depleting effects of METH on striatal DA levels (Bowyer et al. 1992). This effect could also be observed with other amphetamines and in other species. Studies with mice demonstrated that the S-(+) enantiomers of METH, MDA, and MDMA, but not d-fenfluramine, produced damage to dopaminergic projections of the striatum (Miller and O'Callaghan 1994). Importantly, the same study verified an elevation in core temperature associated with exposure to the active S-(+) enantiomers of METH, MDA, and MDMA, whereas exposure to d-fenfluramine lowered core temperature. The same authors used the levels of striatal DA and glial fibrillary acidic protein (GFAP) as indicators of neurotoxicity. Mice treated at 22°C ambient temperature with S-(+)-METH (10 mg/kg), -MDA (20 mg/kg), or -MDMA (20 mg/kg) every 2 h, for a total of 4 s.c. injections, showed an increase in core temperature and caused large (>75%) decreases in striatal DA and large (>300%) increases in striatal GFAP 72 h after the last injection. Lowering ambient temperature from 22 to 15 °C blocked (for MDA and MDMA) or severely attenuated (for METH) these effects (Miller and O'Callaghan 1994). Another report stated that small changes in ambient temperature produced marked changes in the neurotoxicity of MDMA (Malberg and Seiden 1998). Rats treated with MDMA (20 or 40 mg/kg) at ambient temperatures of 20–24°C did not present serotonergic neurotoxicity in the frontal cortex, somatosensory cortex, hippocampus, or striatum. However, at ambient temperatures of 26–30°C, neurotoxicity was seen and correlated with core temperature in all regions examined (Malberg and Seiden 1998).

Many drugs that could prevent or attenuate neurotoxic events also attenuated the hyperthermia elicited by the tested amphetamine. In rats, the non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist dizocilpine blocks depletion of 5-HT induced by METH and p-chloroamphetamine (Farfel and Seiden 1995). The coadministration of METH or p-chloroamphetamine with dizocilpine results in hypothermia, which can attenuate the neurotoxic effects. In mice, the antagonist of glutamate receptors dizocilpine blocked S-(+)-METH-induced, -MDA-induced, and -MDMA-induced neurotoxicity, but promoted hypothermia. When the ambient temperature was elevated during this co-treatment, the neuroprotective effects of the antagonist were markedly attenuated. Therefore, lowering the ambient temperature and pre-treatment with drugs that cause

hypothermia in the mouse are able to prevent or lower very significantly the toxic effects of amphetamines (Miller and O'Callaghan 1994). Thus, many pharmacological compounds that were considered neuroprotectors were also shown to lower the core body temperature. Therefore, these compounds promote a protective effect, not by a specific pharmacological effect, but simply because they interfere with the hyperthermic effect elicited by amphetamines.

Glutamate is the most abundant excitatory amino acid in the CNS and is capable of producing neuronal damage, which is defined as excitotoxicity (Yi and Hazell 2006). Several studies were designed to evaluate the role of excitotoxicity in the neurotoxic effects of amphetamines. One study evaluated the consequence of repeated administration of either METH (7.5 mg/kg; 3 doses every 2 h, i.p.) or MDMA (13.8 mg/kg; 3 doses every 2 h, i.p.) on the extracellular concentrations of glutamate in freely moving rats, using in vivo microdialysis. These doses were previously reported to promote neurotoxicity to the striatum. The authors reported that METH increased the extracellular concentration of glutamate in the striatum, whereas MDMA did not (Nash and Yamamoto 1992). It was reported that rats after a single neurotoxic dose of AMPH (30 mg/kg, i.p.) did not change glutamate levels, but increased both glutamine content and glutamine/glutamate ratio 4 h after treatment, in the caudate-putamen, frontal cortex, and hippocampus (Pereira et al. 2008). These data argue for an increase in the glutamate-glutamine cycle between neurons and glia promoted by AMPH neurotoxic doses. The importance of glutamate in the neurotoxicity of amphetamines was highlighted by the fact that antagonists of glutamate receptors can partially prevent it. This was clearly observed in a previous study with METH-treated mice using an experimental paradigm that produces substantial neurotoxicity (5 mg/kg, i.p.; three injections at 2 h intervals), with massive degeneration of striatal dopaminergic terminals, associated with reactive gliosis (Battaglia et al. 2002). In this study, potent and selective non-competitive mGlu5 receptor antagonists could attenuate METH-induced effects, without interfering with body temperature (Battaglia et al. 2002).

When testing the neuroprotective effects of glutamate or 5-HT receptor antagonists on amphetamines neurotoxic actions in animals, there is the confounding factor of hypothermia promoted by these antagonists. As mentioned above, dizocilpine lowers the core body temperature of animals. Using an in vitro approach, one can circumvent this problem. Our laboratory studies, in cultured rat cortical neurons, demonstrated that MDMA-induced neuronal death was partially prevented by the NMDA receptor antagonist dizocilpine, in both normothermic (37°C) and hyperthermic (40°C) conditions (Capela et al. 2006b). These data suggest

the involvement of excitotoxicity in MDMA-induced neuronal death. Also, using the same in vitro model, we have shown that the selective 5-HT_{2A}-receptor antagonists ketanserin and R-96544 afforded protection against MDMA-induced death of cortical neurons, in a temperature-independent manner (Capela et al. 2007a; Capela et al. 2006b). Indeed, MDMA might elicit glutamate excitotoxicity either directly or indirectly via 5-HT_{2A}-receptor-mediated cell death (Capela et al. 2006b). Moreover, in the case of MDMA, the direct agonism to the 5-HT_{2A}-receptor can promote neuronal death, which can be prevented by 5-HT_{2A}-receptor antagonists (Capela et al. 2007a).

Another important finding that has been revealed by several studies is that selective blockade of monoamine transporters can greatly attenuate or even prevent the neurotoxic actions of amphetamines. These uptake inhibitors do not alter the animal body temperature and do not reverse hyperthermia promoted by amphetamines. Adult rats were treated with METH (10 mg/kg, i.p.) 4 times at 2 h intervals, and 3 days later, it could be observed the typical depletion of dopaminergic terminals and reduction of DA content and astrogliosis in the neostriatum (Pu et al. 1994). In the same study, amfonelic acid (20 mg/kg, i.p.), a DA reuptake inhibitor, administered at the same time of the last METH dose, completely prevented its effects on the dopaminergic system, both morphologically and biochemically (Pu et al. 1994). The importance of the DA transporter in mediating the neurotoxic effects of METH was tested in mice lacking DAT. In wild-type (WT) mice, 4 injections of METH (15 mg/kg, s.c.), each given 2 h apart, caused 80 and 30% decrease in striatal DA and 5-HT levels, respectively, and increased free radical formation 2 days after administration (Fumagalli et al. 1998). Conversely, no significant changes were observed in total DA content, extracellular DA levels, or free radical formation in the striatum of DAT-null mice after METH administration. These observations demonstrate that DAT is required for METH-induced striatal dopaminergic neurotoxicity (Fumagalli et al. 1998). Also in the case of AMPH, the DAT blocker nomifensine protected against AMPH-induced long-term DA depletion in rats (Wan et al. 2000b). Also for MDMA, the 5-HT transporter seems crucial for the serotonergic neurotoxicity of the drug. Administration of fluoxetine (10 mg/kg × 2, i.p.) or fluvoxamine (15 mg/kg × 2, i.p.) to rats provided complete protection against serotonergic neurotoxicity verified in the cortical, hippocampal, and striatum brain areas after MDMA (15 mg/kg, i.p.) (Sanchez et al. 2001). In another report, the administration of fluoxetine (10 mg/kg, i.p.) 4 h after MDMA (20 mg/kg, s.c.) provided full protection against MDMA-induced serotonergic neurotoxicity in rats (Shankaran et al. 1999).

Another important contributing factor for amphetamines neurotoxicity is oxidative stress. Amphetamines have been shown to promote oxidative stress in the brain of experimental animals and cultured neuronal cells, and antioxidants can attenuate their neurotoxic actions. In the rat brain pretreated with desipramine (10 mg/kg, i.p.), an agent that inhibits the metabolism of AMPH, the levels of 2,3-dihydroxybenzoic acid (2,3-DHBA), lipid peroxidation, and DA in striatal homogenates were examined 7 days after injection of a single large dose of AMPH (7.5 mg/kg, i.p.) (Wan et al. 2000a). This study showed that, in the striatum, 2,3-DHBA, and lipid peroxidation were significantly increased by AMPH, whereas DA and its metabolites, DOPAC and HVA, were depleted (Wan et al. 2000a). Another study also proved that AMPH induced HO[•] formation in the rat striatum, an effect that might be DA related and contributes to AMPH-induced neurodegeneration (Huang et al. 1997). The contribution of free radical formation for the neurotoxic actions of amphetamines has also been confirmed by the protection afforded by the free radical scavengers *a*-phenyl-*A*-tert-butyl nitron (PBN) and N-acetylcysteine (NAC) on AMPH neurotoxicity. In rats, both antioxidants could significantly attenuate the long-term DA depletion and lipid peroxidation in the striatum at a dose range that did not block hyperthermia (Wan et al. 2006). Moreover, these two neuroprotective agents completely inhibited the production of HO[•] after AMPH infusion into the striatum (Wan et al. 2006).

Methamphetamine was also shown to elicit pro-oxidant processes. In rats, a dose of 10 mg/kg (+)-METH administered i.p. every 2 h over an 8-h period increased lipid peroxidation and also the formation of the hydroxylated products of salicylate and D-phenylalanine, as evidenced by the elevated extracellular concentrations of 2,3-DHBA and p-tirosine, respectively (Yamamoto and Zhu 1998). In this study, a local perfusion of the iron chelator deferoxamine into the striatum attenuated the long-term depletions of striatal DA content produced by METH. Moreover, pretreatment with the spin-trapping agent phenylbutylnitron before the METH injections attenuated the subsequent long-term depletions in striatal DA content (Yamamoto and Zhu 1998). Additionally, oxidative DNA damage was also reported after METH. Pregnant CD-I mice were treated with a single dose of METH (20 or 40 mg/kg i.p.) on gestational day 14 or 17 resulting in enhanced DNA oxidation by at least twofold, determined by 8-oxoguanine formation, in brain and liver, at 1-h fetal brains (Jeng et al. 2005). Formation of RNS was also reported in the brain of animals treated with METH. Mice treated with multiple doses of METH (4 × 10 mg/kg, 2 h interval) showed increased levels of 3-nitrotyrosine (3-NT) in the striatum as compared with the controls (Imam et al. 2001). In the same

study, no significant production of 3-NT was observed either in the striata of neuronal nitric oxide synthase knockout mice (nNOS^{-/-}) or copper-zinc superoxide dismutase-overexpressed transgenic mice (SOD-Tg) treated with similar doses of METH. The dopaminergic damage induced by METH treatment was also attenuated in nNOS^{-/-} or SOD-Tg mice. The authors clearly confirmed that METH causes its neurotoxic effects via the production of ONOO[•] (Imam et al. 2001).

Several studies have also confirmed the important role of ROS formation in MDMA neurotoxicity (Colado et al. 1997, 1999; Shankaran et al. 1999). Administration of MDMA (15 mg/kg, i.p.) to rats increased the formation of hydroxylated products of salicylate in the hippocampus, which was prevented by the free radical scavenging agent PBN (120 mg/kg, i.p.) (Colado et al. 1997). In a recent study, it was reported that adolescent rats (post-natal day 40, which corresponds to the human adolescence period) exposed to a neurotoxic binge administration of MDMA (10 mg/kg, i.p. 4 times, every 2 h) promoted oxidative stress to whole-brain mitochondria (Alves et al. 2007). Moreover, previous inhibition of MAO-B by selegiline (2 mg/kg, i.p.), at a dose that did not modify hyperthermia, blocked MDMA-induced pro-oxidant deleterious effects to the mitochondria, namely lipid and protein peroxidation and mitochondrial DNA deletions (Alves et al. 2007). This finding argues for an important role of MAO-mediated metabolism of monoamines on MDMA neurotoxicity.

These *in vivo* findings have been also corroborated by cell culture studies. In human neuroblastoma SH-SY5Y cells, METH induced a decrease in mitochondrial membrane potential and an increase in the levels of ROS, as well as a decrease in mtDNA copy number and mitochondrial proteins per mitochondrion. Importantly, in the same study, the same authors reported that vitamin E attenuated METH-induced increase in intracellular ROS levels and mitochondrial mass and prevented METH-induced cell death (Wu et al. 2007). Also works from our group have proven that antioxidants can attenuate the neuronal death promoted by MDMA, or their metabolites, in cultured cortical neurons (Capela et al. 2006b, 2007b).

From the above-mentioned studies, it is possible to conclude that ROS/RNS have an important role in the neurotoxic effects of amphetamines. The origin of these ROS/RNS is still a matter of debate, but clearly two important sources of ROS are the catecholamine auto-oxidation process and the formation of hydrogen peroxide in the event of monoamine oxidation by MAO (Capela et al. 2009). Concerning RNS, as previously described, formation of reactive nitrogen species was reported in the brain of animals treated with amphetamines. NO can be formed in the brain of animals and then react with

superoxide to form ONOO[·], a damaging neurotoxin (Capela et al. 2009). In contrast to other amphetamines, MDMA metabolism leads to the production of several highly reactive metabolites, namely quinone intermediates, which can also promote the formation of ROS and consequent oxidative stress. In cultured cortical neurons of the rat, the neurotoxicity of nine MDMA metabolites: N-Me-a-MeDA, a-MeDA, and their correspondent GSH and NAC adducts was studied (Capela et al. 2006a, 2007b). These studies confirmed the toxicity of MDMA catechol metabolites, N-Me-a-MeDA and a-MeDA (100–800 pM), which showed higher toxicity, compared to the parent compound MDMA. Both N-Me-a-MeDA and a-MeDA, like MDMA, induced programmed neuronal death, during long periods of exposure (48 h) (Capela et al. 2006a). The neurotoxicity of MDMA metabolites was partially prevented by the antioxidant NAC and potentiated under hyperthermic conditions. In subsequent studies, it was tested the neurotoxicity of GSH and NAC conjugates of the catechols N-Me-a-MeDA and a-MeDA (Capela et al. 2007b). GSH and NAC conjugates of N-Me-a-MeDA and a-MeDA induced a delayed concentration-dependent neuronal death, accompanied by activation of caspase 3, which occurred earlier in hyperthermic conditions. Furthermore, thioether MDMA metabolites time-dependently increased the production of pro-oxidant reactive species, concentration-dependently depleted intracellular GSH, and increased protein-bound quinones. In this study, NAC prevented the oxidative stress and neuronal death. Thus, it was clearly shown that MDMA metabolites are more toxic than MDMA and that the conjugates of GSH and NAC catechols, N-Me-a-MeDA and a-MeDA, are significantly more neurotoxic than the non-conjugates. Importantly, several studies in laboratory animals have confirmed the neurotoxic potential of MDMA metabolites (Escobedo et al. 2005; Jones et al. 2005; Miller et al. 1996). Later, the presence of such metabolites was unequivocally demonstrated in the brain of animals after the administration of MDMA (Jones et al. 2005). N-Me-a-MeDA administrated i.p. to mice provoked long-term DA and 5-HT depletion (Escobedo et al. 2005). Intracerebroventricular (ICV) injections of 5-(NAC)-a-MeDA and 5-(GSH)-a-MeDA into rats produced neurobehavioral changes similar to those seen after peripheral administration of MDMA/MDA, as well as acute increases in brain 5-HT and DA concentrations (Miller et al. 1996). Another MDMA metabolite, 5-(NAC)-N-Me-a-MeDA, also produced acute behavioral changes in rats similar to those seen after peripheral administration of MDMA, and importantly, significantly decreased striatal and cortical concentrations of 5-HT and 5-hydroxyindoleacetic acid (5-HIAA) in a dose-dependent manner (Jones 2005). From the above-mentioned studies, it is possible to conclude that MDMA metabolism leading to

reactive thioether MDMA metabolites plays an essential role in the neurotoxic events mediated by MDMA.

Neurotoxicity of amphetamines in humans

Studies in humans are of striking importance to provide indication of doses or frequency regimens that may put amphetamines users at risk of neurotoxicity. Given the limitations of extrapolating the results obtained in animal studies to the human situation, the definitive confirmation of amphetamines neurotoxic actions can only be revealed by human studies. Studies on the long-term effects of amphetamines on monoaminergic neurotransmission in humans are rather based on indirect methods. These reports evaluate the levels of monoamines or their metabolites or use neuroimaging techniques to reveal the number of transporter binding sites. Also, other studies in humans try to correlate deficits in memory and learning with the extent of drug abuse.

It is known that the sustained use of AMPH can promote psychosis in normal subjects, uniquely resembling the paranoid form of schizophrenia, as a possible result of neurotoxic actions of the drug (Vollenweider et al. 1998). In 10 healthy human volunteers, the effects of high euphorogenic doses of d-AMPH (0.9–1.0 mg/kg p.o.) on regional cerebral glucose metabolism were investigated using PET (Vollenweider et al. 1998). The study reported increases in cortical and subcortical cerebral metabolism after d-AMPH administration in humans, demonstrating that relatively high doses (presumably at least 1 mg/kg) are needed to increase cerebral glucose metabolism (Vollenweider et al. 1998). Another study using functional magnetic resonance imaging was developed to examine the effects on motor and verbal skills, memory, and spatial attention task in 18 healthy volunteers (Willson et al. 2004). Functional measurements were obtained at baseline and again at 75 min after an oral dose of 25 mg d-AMPH, which promoted decreases in brain activity in several regions during cognitive tasks. These changes may possibly be mediated by alterations in dopaminergic activation caused by the drug (Willson et al. 2004).

Human neuroimaging findings suggest that METH is neurotoxic and may lead to significant alterations in brain structures, accompanied by alterations in brain metabolism and microvasculature (Schwartz et al. 2010; Thompson et al. 2004b). One study published in 1996 in *Nature Medicine* reported reduced levels of three DA nerve terminal markers (DA, TH, and DAT) in post-mortem striatum (nucleus accumbens, caudate, putamen) of chronic METH users (Wilson et al. 1996). However, the authors suggested these depletions were not related to degeneration of striatal dopamine nerve terminals (Wilson et al. 1996). Using magnetic resonance imaging and new computational

brain-mapping techniques, a more recent study showed that METH users had 7.8% smaller hippocampal volumes than control subjects and significant white matter hypertrophy. The authors also report that METH may selectively damage the medial temporal lobe and, consistent with metabolic studies, the cingulate-limbic cortex (Thompson et al. 2004b). A more recent study suggested that the early use of METH (in subjects who initiated use before the age of 21) was associated with smaller intracranial volume (Schwartz et al. 2010). Also using neuroimaging techniques, a very recent study showed that METH users had enhanced cortical grey matter volume loss with age in the frontal, occipital, temporal, and the insular lobes, compared to controls, independently of METH usage patterns (Nakama et al. 2011). Additionally, METH users showed smaller grey matter volumes than control subjects in several brain regions. The authors concluded that METH users appear to show increased cortical grey matter loss with age, which raises the possibility of accelerated decline in mental function (Nakama et al. 2011).

The cerebral spinal fluid (CSF) of recreational MDMA users, which had used “ecstasy” on more than 25 occasions, showed significantly lower levels of 5-HIAA compared to control subjects (McCann et al. 1994, 1999). Another report showed that MDMA users displayed multiple regions of grey matter reduction in the neocortical, bilateral cerebellum, and midline brainstem brain regions, potentially accounting for previously reported neuropsychiatric impairments in MDMA users (Cowan et al. 2003). Neuroimaging techniques, like PET, were used in combination with a 5-HTT ligand in human “ecstasy” users, showing lower density of brain 5-HTT sites (McCann et al. 1998, 2005, 2008). Other authors correlate the 5-HTT reductions with the memory deficits seen in humans with a history of recreational MDMA use (McCann et al. 2008). A recent study prospectively assessed the sustained effects of “ecstasy” use on the brain in novel MDMA users using repeated measurements with a combination of different neuroimaging parameters of neurotoxicity. The authors concluded that low MDMA dosages can produce sustained effects on brain microvasculature, white matter maturation, and possibly axonal damage (de Win et al. 2008). More recently, 5-HTT binding was measured in 50 control subjects and in 49 chronic (mean 4 years of abuse) MDMA users (typically one to two tablets bi-monthly) abstinent from the drug (mean 45 days of abstinence) (Kish et al. 2010). The authors suggested that the “typical”/low-dose (one to two tablets/session) chronic MDMA user might display a highly selective mild to marked loss of 5-HTT in cerebral cortex/hippocampus (Kish et al. 2010).

One must bear in mind that most studies in humans are retrospective and conducted with polydrug users, which is always a confounding factor. Also, the amount

of drug used by each user differs greatly, and the participants in these studies are very heterogeneous. Despite all the difficulties regarding studies in humans, the vast majority of reports provide data to support the idea that amphetamines can promote deleterious effects to the human brain.

Unsolved issues regarding the neurotoxicity of amphetamines

Despite the huge amount of research on the neurotoxicity of amphetamines, much is still to be clarified. Indeed, the neurotoxicity found in studies with laboratory animals cannot be directly extrapolated to the human situation. The long-term neurotoxic effects, reported by many, are rather regarded by some authors as brain adaptations and not real neurotoxic events. Moreover, the neurotoxic mechanisms of amphetamines are still a matter of debate (Capela et al. 2009).

Several questions remain to be answered:

- Despite distal axotomy of monoaminergic neurons seen in many studies, which was not proven to be fully reversible, are monoamine depletions produced by several amphetamines real measures of neurotoxicity or transitory events?
- How can pharmacokinetic differences among species, and especially among laboratory animals and humans, explain differences in terms of susceptibility toward neurotoxicity?
- Can we circumvent the problem of polydrug abuse to definitively confirm the neurotoxic events of amphetamines in human subjects?
- What are the actions of amphetamines to the young brain as a result of intake by children or adolescents and their consequences in brain aging?
- What therapeutic strategies can be implemented to prevent and treat the neurotoxic events elicited by amphetamines?

Liver toxicity

Hepatocellular injury caused by amphetamines has been known since the beginning of its therapeutic use. The first publication related to hepatotoxicity in laboratory animals dates from 1939 (Ehrlich et al. 1939). Harvey and coworkers in 1949 reported a fatal case of centrilobular necrosis after ingestion of the contents of two inhalers containing 250 mg of AMPH each (Harvey et al. 1949). These initial reports were followed by many others that became undisputed evidence of the existence of a cause-effect relationship between AMPH abuse and hepatotoxicity, both in experimental

animals (Zalis et al. 1967) and in man (Jones et al. 1994; Kalant and Kalant 1975; Zalis and Parmley 1963). Hepatocellular damage can occur with both acute and chronic AMPH abuse (Henry et al. 1992; Jones et al. 1994; Khakoo et al. 1995).

Because most studies on the liver toxicity of the amphetamines address MDMA hepatotoxicity, this drug will be especially envisaged in the following sections.

MDMA hepatotoxicity

The widespread use of MDMA as a recreational drug has been responsible for the appearance of several cases of acute liver failure in young people. The first cases of hepatotoxicity associated with the consumption of ecstasy were described in 1992 by Henry and coworkers, followed by many others that confirmed this association (Andreu et al. 1998; Coore 1996; Dykhuizen et al. 1995; Fidler et al. 1996; Jones et al. 1994). In fact, MDMA was reported as the second most common cause of liver injury (after ethanol) in young people admitted to an intensive care unit in Spain (Andreu et al. 1998), with clinical features ranging from benign forms, indistinguishable from acute viral hepatitis (Dykhuizen et al. 1995; Ellis et al. 1996), to severe forms, such as liver dysfunction due to extensive and/or focal hepatic necrosis (Henry et al. 1992; Milroy et al. 1996), or even fulminant hepatic failure requiring urgent liver transplantation (Brauer et al. 1997; Caballero et al. 2002; Ellis et al. 1996; Garbino et al. 2001; Liechti et al. 2005). In fact, after exposure to MDMA, the liver can show dramatic changes. A fairly constant pattern consisting of alterations in normal hepatic architecture due to necrosis is usually observed. Necrosis can be focal, especially in the centrilobular zone, or extensive to midzonal regions and is usually accompanied by an acute inflammatory response surrounding necrotic hepatocytes. Fatty changes and sinusoidal dilatation are also occasionally observed. Cholestatic hepatitis was reported in some cases (Andreu et al. 1998; Ellis et al. 1996; Hall and Henry 2006; Milroy et al. 1996). Khakoo and coworkers reported a case of accelerated hepatic fibrosis following ecstasy abuse (Khakoo et al. 1995). In some patients with MDMA-related acute hepatitis, the portal tracts are expanded by edema and inflammatory infiltrates. In addition, focal hepatocellular necrosis and microvesicular fatty changes were observed in preserved hepatocytes at periportal areas (Andreu et al. 1998). The hepatocellular injuries observed in MDMA-intoxicated patients are very similar to those observed in heatstroke (Wills et al. 1976) and are probably related with the increase in body temperature induced by MDMA. In fact, several subjects who developed hepatic damage after taking ecstasy were hyperpyrexial for many hours (Ellis et al. 1996; Henry et al. 1992). Therefore, it has been

hypothesized that these hepatotoxic effects may be caused by circulatory collapse and hypoxic damage, most probably combined with disseminated intravascular coagulation (DIC) that is a common complication of heatstroke (Mustafa et al. 1985). On the other hand, in some cases where liver damage appears unrelated to hyperpyrexia, it is unclear whether the damage is caused by an idiosyncratic reaction to MDMA, interindividual variability, and/or a contaminant of the drug (Milroy et al. 1996).

Some aspects of the pathogenesis of liver injury associated with amphetamines remain poorly understood, such as the variability in the delay between the drug consumption and the onset of the first symptoms. In most reported cases, the interval was of a few days, but in others, it was 2 or 3 weeks (Henry 1992). Moreover, the severity of the symptoms and the hepatic lesions do not seem to correlate either with the duration of use or with the amount of drug consumed (Andreu et al. 1998; Dykhuizen et al. 1995; Garbino et al. 2001). In some cases, liver damage occurred after the ingestion of one or two tablets, while in others, it appeared only after regular use for weeks or months. As worst case examples, two cases of fulminant hepatitis (Coore 1996; Ellis et al. 1996) and two cases of acute hepatitis (Dykhuizen et al. 1995; Henry et al. 1992) have been reported after ingestion of a single tablet of ecstasy.

In agreement with the clinical literature, in vivo studies in an animal model revealed multiple foci of frank liver cell necrosis and areas with multiple microvesicles in the cellular cytoplasm after MDMA administration (Johnson et al. 2002b). In another study in mice, lysosomal activation, mitochondrial swelling, intracellular edema, and some isolated necrotic cells were observed in liver sections, causing increased levels of plasma transaminases (Pontes et al. 2008a). In rats, apoptosis was seen in the liver 72 h after ecstasy use (Warren et al. 2006), corroborating previous in vitro findings in rat-isolated hepatocytes (Montiel-Duarte et al. 2002) and in cultured hepatic stellate cells (Montiel-Duarte et al. 2004). The induction of apoptosis was accompanied by a reduction in the antiapoptotic protein Bc 1-x₁, mitochondrial release of cytochrome c, and caspase-3 activation. Moreover, MDMA has been shown to induce collagen production on hepatic stellate cells at low concentrations (Varela-Rey et al. 1999). In another in vivo study in rats, MDMA treatment caused cell necrosis particularly in portal areas with inflammatory infiltrate consisting in lymphocytes and macrophages denser in portal tracts, especially after repeated MDMA administration (Beitia et al. 2000). This hepatotoxicity seems to be associated with an increased index of lipid peroxidation and decreased GSH levels (Beitia et al. 2000; Carvalho et al. 2002a; Johnson et al. 2002b; Ninkovic et al. 2004), and the susceptibility to these effects seems to be increased by

antioxidant deficiency (Johnson et al. 2002b), thus suggesting that MDMA can induce oxidative stress in the liver.

Mechanisms of amphetamines hepatotoxicity

The mechanisms involved in liver damage induced by amphetamines are complex and still not completely understood. A variety of hypothesis have been proposed including the increased efflux of neurotransmitters, the oxidation of biogenic amines, hyperthermia, a possible direct effect of amphetamines and/or reactive metabolites, the phenomenon of mitochondrial impairment, and apoptosis [reviewed in (Carvalho et al. 2010)]. In addition, genetic polymorphism of metabolizing enzymes (particularly CYP2D6), polydrug abuse, and environmental features accompanying illicit amphetamine use may increase the risk for liver complications.

Metabolism seems to be an important factor in the induction of hepatic injury. It has been shown that d-AMPH is activated by CYP2D isoenzymes into a reactive intermediate (probably an epoxide), which reacts with GSH to form (glutathione-S-yl)-p-hydroxyamphetamine. Our group previously described that d-AMPH depletes GSH levels in the mouse liver (Carvalho et al. 1993) and in freshly isolated rat hepatocytes (Carvalho et al. 1996, 1997), which was prevented by pre-treatment with the CYP inhibitor metyrapone (Carvalho et al. 1996).

Similar to d-AMPH, MDMA is metabolized with formation of GSH conjugates, namely 2-(glutathione-S-yl)-a-MeDA, 5-(glutathione-S-yl)-a-MeDA, and 2,5-bis(glutathione-S-yl)-a-MeDA (Carvalho et al. 2004a; Hiramatsu et al. 1990; Miller et al. 1997). However, the mechanism of formation of these adducts differs from the one proposed for d-AMPH because it involves the formation of a catechol, which after oxidation to quinone reacts rapidly with thiol groups (Fig. 5). The potential role of the oxidative metabolites in MDMA-elicited hepatotoxicity was studied for the first time by our group using freshly isolated rat hepatocyte suspensions as *in vitro* model (Carvalho et al. 2004a, b). In these studies, the effects of MDMA and its major hepatic-derived metabolites MDA, N-Me-a-MeDA, and a-MeDA on cell viability, GSH levels, and on the activities of GR, GPX, and GST were evaluated. MDMA and the N-demethylated metabolite MDA induced a time- and concentration-dependent GSH depletion, but had a negligible effect on cell viability, or on the antioxidant enzymes activities. GSH depletion following MDMA exposure has been reported in several other studies conducted in mice (Carvalho et al. 2001) and rat (Beitia et al. 1999; Pontes et al. 2008b) hepatocytes. Glutathione depletion was clearly enhanced upon exposure to the demethylenated metabolites N-Me-a-MeDA and a-MeDA and accompanied by a loss in cell viability and decreases in

the antioxidant enzyme activities. GSH plays a crucial role in the processes of cellular protection against electrophilic compounds, ROS, and RNS formed within the cells (DeLeve and Kaplowitz 1991).

In spite of the different mechanisms involved, it seems that depletion of hepatic GSH levels may be an initial step for the hepatotoxic action reported for different amphetamines. Disruption in thiol redox homeostasis may result in loss of protein function and initiation of a cascade of events leading to oxidative damage. In accordance, our group showed that ascorbic acid or NAC prevented cell death and GSH depletion induced by N-Me-a-MeDA in rat hepatocytes (Carvalho et al. 2004b). Depletion of hepatic GSH in cells exposed to amphetamines did not lead to an alteration in cell viability or lipid redox status (Carvalho et al. 1996, 2004a, b), but disruption of liver GSH status may most likely affect susceptibility to amphetamines when cells are exposed to other toxic insults that occur simultaneously *in vivo* as, for example, hyperthermia.

In fact, since hyperthermia and metabolism of amphetamines occur *in vivo*, it seems reasonable to surmise that these situations are potentially lethal and most certainly contribute to the hepatotoxicity that has been reported in humans. The influence of hyperthermia in amphetamines hepatotoxicity was evaluated by our group in freshly isolated rat (Carvalho et al. 1997) and mouse hepatocytes (Carvalho et al. 2001) and, more recently, in primary cultured rat hepatocytes (Pontes et al. 2008b). In all cell models, hyperthermic conditions potentiated the hepatotoxic effects of amphetamines namely those related to oxidative stress: depletion of GSH levels, lipid peroxidation, and loss of cell viability.

Recent studies have suggested that mitochondria may be important target organelles for MDMA hepatotoxicity (Burrows et al. 2000; Moon et al. 2008; Nakagawa et al. 2009). A recent study conducted by Nakagawa and coworkers shows that the exposure of isolated hepatic mitochondria to MDMA causes mitochondrial impairment and induction of the mitochondrial permeability transition (MPT) accompanied by mitochondrial depolarization and depletion of ATP through uncoupling of oxidative phosphorylation (Nakagawa et al. 2009). It was previously shown by Beitia and coworkers that MDMA induces a concentration- and time-dependent ATP depletion in isolated rat hepatocytes (Beitia et al. 1999).

Generation of ROS may play a role in mitochondrial dysfunction (Brown and Yamamoto 2003). However, it is still unknown whether the generation of ROS in hepatocytes incubated with MDMA depends on either disturbance of the mitochondrial respiratory chain or redox cycles formed between o-quinones and their semiquinones derived from MDMA metabolism. On the other hand, it is plausible that MDMA and/or its reactive metabolites

(especially the quinone metabolites) may inhibit the mitochondrial function by directly interacting with mitochondrial proteins, as recently demonstrated with cytochrome c (Fisher et al. 2007). In addition, MDMA metabolites can indirectly cause mitochondrial dysfunction through increased oxidative/nitrosative stress. Moon and coworkers have shown that MDMA causes oxidative inactivation of key mitochondrial enzymes, which most likely leads to mitochondrial dysfunction and subsequent liver damage. Among these, the activities of mitochondrial 3-ketoacyl-CoA thiolases (involved in ATP production via the fat degradation pathway) and ATP synthase were significantly inhibited following MDMA exposure (Moon et al. 2008), suggesting that hepatocytes may not properly carry out many cellular functions and eventually undergo the necrotic cell death process.

The effects caused by the consumption of amphetamines can be conditioned by a plethora of factors that converge in a certain individual on a certain moment. In addition to the specific factors raised previously, behavioral and environmental factors accompanying illicit amphetamine use may increase the risk for liver complications. For instance, MDMA has become a popular recreational drug of abuse at nightclubs and rave or techno parties, where it is combined with intense physical activity ("all-night dancing"), crowded conditions (aggregation), high ambient temperature, poor hydration, loud noise, and is commonly taken together with other stimulant "club drugs" and/or alcohol (Parrott 2006; Von Huben et al. 2007; Walubo and Seger 1999). This combination is probably the main reason why it is generally seen an increase in toxicity events at rave parties since all these factors are thought to induce or enhance the toxicity (particularly the hyperthermic response) of MDMA.

Finally, one should keep in mind that amphetamine street drugs such as ecstasy are manufactured in clandestine laboratories and the content of drug tablets is often dependent on the source (EMCDDA 2007). Thus, the possible presence of potentially hepatotoxic contaminants in the individual batch of the drug can never be excluded.

Cardiotoxicity of amphetamines

The cardiovascular toxicity of amphetamines results mostly from the increased release of catecholamines and 5-HT into the synaptic cleft and the blood stream (Milroy et al. 1996). As noted above, amphetamines act as highly potent releasers of monoamines in the CNS. Although the cardiovascular system is mainly regulated by the autonomic system, the CNS pathways can easily interfere with cardiac homeostasis (Costa et al. 2011). Importantly, the NA pathways of the brain play a crucial role in the regulation of cardiovascular functions (Costa et al. 2011).

In addition, recent evidence points to the involvement of secondary mechanisms in the development of amphetamine-induced cardiotoxic effects, including metabolic bioactivation and hyperthermia. The cardiovascular effects reported for the three drugs envisaged by this review are summarized below.

Amphetamine cardiotoxicity

Amphetamine is a sympathomimetic agent that stimulates catecholamine release, particularly DA and NA, from the pre-synaptic nerve terminals. The plasma membrane uptake transporters and the monoamine secretory/synaptic vesicles are involved in AMPH actions (Sulzer et al. 2005). Several experiments with different study models (e.g., *in vivo*, using electrochemical detection techniques; using mutated transporters; using reserpine in neuronal cultures) are all consistent with the ability of AMPH to act on both vesicular and plasma membrane transporters, and accordingly, to affect monoamine pools both in synaptic vesicles and within the cytosol (Sulzer et al. 2005). AMPH also inhibits MAO in perfused rat heart (Leitz and Stefano 1971), although the catecholamine levels only increase significantly when this inhibition is combined with the inhibition of VMAT (Costa et al. 2011). AMPH was recognized as a VMAT2 inhibitor, although Brown and coworkers suggested that the response to amphetamines is indirect and that the apparent inhibition of VMAT2 is due to D₂ autoreceptor activation following DA release (Brown et al. 2002). The activation of the D₂ autoreceptors led to VMAT2 redistribution to endosomes or other compartments (Brown et al. 2002).

Peripherally, AMPH-mediated release is greater for NA than DA (Florin et al. 1994). In addition, d-AMPH is a potent inhibitor of NA reuptake, which may be the basis for its greater potency over the R-(—) enantiomer (Sulzer et al. 2005). Reporting to the interference of neurotransmitters or hormones, which can have direct or indirect actions on cardiac function, AMPH increased extracellular NA in the brain of male Sprague-Dawley rats (Florin et al. 1994). Furthermore, AMPH increases extracellular NA through reuptake blockade, which predominates at lower doses, or through the release of NA, which becomes more prevalent at higher doses. In rat brain slices, AMPH was shown to raise extracellular DA levels by inducing stimulation-independent DA efflux via reverse transport through the DA transporter and by inhibiting DA re-uptake (Florin et al. 1994). In contrast, a more recent study indicated that AMPH decreases stimulation-dependent vesicular DA release (Schmitz et al. 2001). Furthermore, AMPH was shown to induce an increase in TH activity (Mandell and Morgan 1970), which further increases the catecholamine availability, and thus, the stimulation of adrenoceptors in

the CNS. This adrenoceptors-stimulation indirectly triggers alterations in the cardiovascular function (Costa et al. 2011). On the other hand, the direct action on heart receptors or the direct action of the molecules on the myocardial tissue can cause stress cardiomyopathy, myocardial infarction, and tachycardia, among other cardiovascular disorders (Costa et al. 2011).

Besides its use as a drug of abuse, AMPH is also presently used as a therapeutic agent in the attention-deficit/hyperactivity disorder and in clinical trials for stroke (Winterstein et al. 2009). Cardiotoxicity (manifested as cardiomyopathy, acute myocardial infarction/necrosis, heart failure, or arrhythmia) after the use or misuse of AMPH has been documented in both situations (Alsidawi et al. 2011; Bashour 1994; Gandhi et al. 2005; Hung et al. 2003; Jacobs 2006; Marks 2008; Smith et al. 1976; Sprigg et al. 2007; Sylvester and Agarwala 2012; Waksman et al. 2001). Presently, most of the reports dealing with severe cardiac effects related to AMPH use arise from its therapeutic use.

The clinical trials and human studies that used AMPH as a therapeutic agent demonstrated several cardiovascular effects. To assess long-term cardiovascular effects of an extended release formulation containing mixed amphetamine salts, a study was performed in 223 otherwise healthy adults with attention-deficit/hyperactivity disorder combined subtype. The patients were exposed up to 24 months to the mixed amphetamine salts extended release formulation (20–60 mg/day). In these doses, mean changes in resting sitting diastolic blood pressure and systolic blood pressure were small and not considered clinically significant within the group analysis. However, seven subjects discontinued the medication due to cardiovascular events, namely hypertension ($n = 5$) and palpitation/tachycardia ($n = 2$) (Weisler et al. 2005). A phase II randomized (1:1), double-blind, placebo-controlled trial was conducted in post-ischemic stroke patients, to determine the effects of AMPH. Thirty-three subjects were recruited, aged 33–88 (mean 71) years, 52% men, 4–30 (median 15) days post-stroke (Sprigg et al. 2007). Sixteen patients were randomized to placebo and seventeen to AMPH treatment. Subjects received d-AMPH (5 mg initially, followed by 10 mg for 10 subsequent administrations with 3- or 4-day intervals) or placebo in addition to inpatient physiotherapy. Peripheral and central systolic blood pressure and heart rate were 11.2 mm Hg ($P = 0.03$), 9.5 mm Hg ($P = 0.04$), and 7 beats per minute ($P = 0.02$) higher, respectively, with AMPH, compared with placebo (Sprigg et al. 2007).

A mixed AMPH salts extended release formulation with the brand name “Adderall XR” commonly prescribed for children and adolescents with attention-deficit/hyperactivity disorder has resulted in several reports of cardiac toxic effects. A 15-year-old boy, without previous known

cardiac abnormalities, suffered a myocardial infarction after starting Adderall XR, which was presumably secondary to an acute vasospasm (Sylvester and Agarwala 2012). In another report, a patient developed cardiomyopathy after receiving a therapeutic course of d-AMPH. The cardiac function of the patient deteriorated to the point of heart failure, which required heart transplantation (Marks 2008).

Takotsubo cardiomyopathy, also known as stress-induced cardiomyopathy, is a severe and reversible left ventricular dysfunction extending beyond the territory of a single epicardial coronary artery in the absence of coronary artery disease or pheochromocytoma. Takotsubo cardiomyopathy has been reported after AMPH use. A 19-year-old girl was diagnosed with Takotsubo cardiomyopathy after ingesting 30 Adderall tablets (Alsidawi et al. 2011). Also, a 25-year-old woman was presented with shortness of breath to the emergency room of a hospital, shortly after inhalation of amphetamines. Her vitals revealed sinus tachycardia of 140 beats per min and elevated blood pressure of 160/90 mmHg with plasma troponin levels of 7 ng/mL and was diagnosed with Takotsubo cardiomyopathy (Movahed and Mostafizi 2008). The etiology of stress cardiomyopathy is still a matter of debate, but it is often suggested to be secondary to a catecholamine surge (Costa et al. 2011), thus corroborating AMPH sympathomimetic effects. In fact, AMPH-induced tachycardia and hypertension could have been the trigger of reverse apical ballooning in these two reports. In conscious coronary sinus-cannulated dogs, the administration of d-AMPH [$0.1 \text{ mg} \times \text{kg}^{-1} \times 10 \text{ min}$ (i.v.)] significantly elevated mean arterial pressure (+30%) and increased coronary sinus and peripheral venous NA concentrations, events that indicate neurotransmitter release in the heart upon AMPH administration (Lynch et al. 2009).

There are several papers reporting AMPH toxicity toward the cardiovascular system in a drug abuse scenario. AMPH causes myocardial infarction, and coronary spasm, among other cardiovascular effects (Bashour 1994; Brennan et al. 2004; Hung et al. 2003; Waksman et al. 2001). Coronary artery rupture associated with AMPH intake caused massive infarction, extremely depressed left ventricular performance, and hemodynamic instability with acute severe pump failure in a 28-year-old man, who required heart transplant (Zebis et al. 2007). After repeated administration of d-AMPH, in a context of drug abuse, a 45-year-old woman developed congestive heart failure (Smith et al. 1976). This woman had no evidence of coronary heart disease, valve disease, or other demonstrable cause of heart failure (Smith et al. 1976). Jacobs reported 6 cases of young persons who died unexpectedly after the chronic abuse of amphetamines. Death causes were not attributed to a lethal intoxication, but to an acute myocardial necrosis, a right ventricle rupture, a

cardiomyopathy, or an arrhythmia, since AMPH consumption was ignored or neglected upon first medical or forensic evaluation (Jacobs 2006).

Methamphetamine cardiotoxicity

Cardiovascular events are frequently involved in the medical complications and fatalities associated with METH abuse. Methamphetamine elicits rapid tachycardia in humans (Perez-Reyes et al. 1991a). In 2005, Newton and coworkers made a study with 11 non-treatment-seeking METH-dependent volunteers, which received a single i.v. 30 mg METH dose. Subjective and cardiovascular responses were assessed for 30 and 60 min and revealed a rapid increase in systolic and diastolic blood pressure, as well as an increase in heart rate that persisted for several hours (Newton et al. 2005a). However, METH use has more drastic consequences than these transient effects. Cerebral stroke, hemorrhage, and hypertension are among the vascular complications associated with METH abuse (Barr et al. 2006; Kaye et al. 2007). Post-mortem studies show that METH causes myocardial infarction, arrhythmias, cardiomyopathy, and ventricular hypertrophy (Bhave and Goldschlager 2011; Hong et al. 1991; Ito et al. 2009; Jacobs 1989; Karch 2011; Yeo et al. 2007). In fact, METH causes cardiovascular problems in young individuals, in which these type of complications are relatively uncommon (Bhave and Goldschlager 2011; Karch 2011; Yeo et al. 2007).

In child-bearing white women in California, the consumption of METH was estimated to be higher than 1% (Vega et al. 1993) and was responsible for maternal deaths due to intracerebral hemorrhage and cardiovascular collapse, among other problems (Catanzarite and Stein 1995). Yeo and coworkers observed an association between METH use and cardiomyopathy in patients with age less than 45 years (Yeo et al. 2007). In their patient cohort, every 4 out of 10 patients with cardiomyopathy aged lower than 45 years had a history of METH use. Most relevant, they concluded that patients with METH-associated cardiomyopathy have a more severe disease compared to other non-ischemic cardiomyopathies. Patients that use METH have a significantly lower left ventricular ejection fraction compared to cardiomyopathy patients without METH use (Yeo et al. 2007). These data suggest that young patients who use METH are not only at a higher risk of developing cardiomyopathy but also of developing a more severe form of cardiomyopathy (Ito et al. 2009; Yeo et al. 2007). Even so, some observations suggest that myocardial pathology may be reversible with early cessation of METH use (Jacobs 1989).

As described for other amphetamines, METH abuse is also often characterized by a repeated pattern of frequent drug use (binge) followed by a period of abstinence. Varner

and colleagues made a “binge” administration of METH to conscious rats (Varner et al. 2002) to mimic the binge METH abuse in humans. The authors used radiotelemetry to record the cardiovascular responses elicited during three successive METH binges (3 mg/kg, twice a day for 4 days). Each binge was followed by a 10-day METH-free period. The heart rate responses elicited by METH were similar within and among the three binges and characterized by pressor effects with biphasic heart rate responses consisting of an initial bradycardia followed by tachycardia (Varner et al. 2002). In rats, the binge administration of METH sensitizes them to the pressor effects of the drug as blood pressure increased in the second and third administration (Varner et al. 2002). This result clearly demonstrates an adaptation of the sympathomimetic system after amphetamines repeated use.

Mechanistically, METH exerts multiple pharmacological effects via different molecular processes as referred in the previous sections. Methamphetamine mainly acts on the CNS causing non-exocytotic release of monoamine neurotransmitters, including DA, NA, and 5-HT (Sulzer et al. 2005). The increased levels of monoamines caused by METH also results from its ability to interfere with monoamine reuptake transporters, decrease the activity of VMAT and MAO, and increase the activity and expression of TH (Brown et al. 2002; Guilarte et al. 2003; Mandell and Morgan 1970; Melega et al. 2008; Sandoval et al. 2003). As a result of these combined mechanisms, METH acts as a highly potent releaser of monoamines in the CNS. Although the cardiovascular system is mainly regulated by the autonomic system, the CNS pathways easily interfere with cardiac homeostasis (Costa et al. 2011). Importantly, the CNS pathways of NA play a crucial role in the regulation of cardiovascular functions (Costa et al. 2011), and as METH affects these pathways, it can be easily understood how METH greatly modifies the cardiovascular system through its action in the CNS.

Methamphetamine has been proven not only to promote neurotransmitter release in the nervous system, but system and several evidences suggest that METH exposure leads to high catecholamines levels in the peripheral organs. Methamphetamine stimulates the release of catecholamines and 5-HT from the adrenal medulla and sympathetic nerve terminals (Makisumi et al. 1998). These events cause activation of central and peripheral α- and β-adrenergic autonomic receptors. Methamphetamine has a significantly greater elimination half-life than many other psychostimulants leading to effects that last substantially longer in all systems (Fowler et al. 2007). Immediate side effects in peripheral organs, which result partly from the effects of METH on adrenaline and NA release by the adrenal glands (Makisumi et al. 1998), may lead to increased blood pressure, hyperthermia, stroke, and cardiac arrhythmia

(Barr et al. 2006; Kaye et al. 2007). Methamphetamine is also a weak inhibitor of MAO (Suzuki et al. 1980) and decreases the activity of VMAT (Brown et al. 2002). The combination of both favors catecholamine accumulation (Costa et al. 2011). Autopsy studies of METH users have shown contraction band necrosis in the myocardium, which is also normally seen after catecholamine toxicity corroborating the biogenic amine involvement (Islam et al. 2009; Karch 2011). Catecholamines excess can conceivably result in cardiomyopathy through recurrent coronary vasospasm, tachycardia, hypertension, accelerated atherosclerosis, and/or direct myocardial toxicity (Costa et al. 2011). Importantly, the surge of catecholamines in the presence of MAO inhibition and/or oxidative stress favors the autoxidation of catecholamines, which potentiates heart injury (Costa et al. 2007, 2011).

Methamphetamine cardiotoxicity is also associated with oxidative damage. A recent publication showed that 4 METH administrations (3 mg/kg, i.v. for 4 days, separated by a 10-day drug-free period) in rats produced eccentric left ventricular hypertrophy, significantly impaired the systolic function (decreased fractional shortening, ejection fraction, and adjusted maximal power), and produced significant diastolic dysfunction (Lord et al. 2010). Dihydroethidium staining showed that METH significantly increased (285%) the levels of ROS in the left ventricle. Treatment with the SOD mimetic, tempol (2.5 mM), in the drinking water prevented METH-induced left ventricular dilation and systolic dysfunction. However, tempol did not prevent the diastolic dysfunction. Also, tempol significantly reduced, but did not eliminate, dihydroethidium staining in the left ventricle, thus showing that oxidative stress plays a significant role in mediating METH cardiotoxicity (Lord et al. 2010). Methamphetamine-induced oxidative damage might be also related to the high levels of catecholamines induced by the interaction of METH with neurotransmitter transporters. Another important factor that may contribute to oxidative stress is inflammation (Islam et al. 2009). The hearts from rats treated with a METH binge administration regimen showed focal inflammatory infiltrates with abundant monocytes and occasional necrotic foci (Varner et al. 2002). The self-perpetuating cycle of inflammation, oxidative stress, and mitochondrial dysfunction initiated by catecholamine release may extend well beyond the acute pharmacodynamic (PD) effects of METH and could represent an underlying and potentially progressive degenerative process. In particular, the mitochondrial dysfunction, the oxidative and nitrosative stress (evaluated by tyrosine nitration) (Lord et al. 2010), and inflammation (Islam et al. 2009; Varner et al. 2002) caused by the METH-induced catecholamine surge is crucial to impair heart function, which is particularly redox sensitive (Costa et al. 2011). It is well known that the phagocytic

response can exacerbate the catecholamine-induced oxidative stress and leads to catecholamine auto-oxidation (Costa et al. 2011), which, on the other hand, causes alterations in cardiac proteins and energetic metabolism (Costa et al. 2007, 2009).

Both enantiomers (11C S-(+)- and R-(—)-METH) showed rapid and high uptake in the heart, as shown by comparative PET studies in non-human primates, which may account for some of the cardiac toxic effects of METH (Fowler et al. 2007). Fowler and coworkers did not observe any significant differences in the distributions of METH enantiomers in the heart. S-(+)-Methamphetamine presented a high initial distribution to the heart (0.059%/cm³ at 0.21 min after injection) and a short residence time in the heart (a half-time of approximately 0.5 min from peak) in baboons (Fowler et al. 2007). In the heart of humans, the cardiac uptake of METH occurred fast, within 55–60 s, while the clearance (half-peak clearance) was intermediate (16 min) (Volkow et al. 2010). The heart has lower total METH uptake than other organs (2.6% of an i.v. injected dose one min after administration), and its maintenance in heart was very short-lasting in humans (Volkow et al. 2010). This was unexpected since cardiovascular events are among the most frequent medical complications reported in METH abusers (Kaye et al. 2007). Nonetheless, the good temporal correspondence between METH fast accumulation in heart (peaks at 60 s) and the fast increase in blood pressure induced by this drug (peaks at 60 s after i.v. administration) (Newton et al. 2005a) suggests that METH may also directly affect cardiac tissue, as demonstrated by studies in cultured adult rat ventricular myocytes (He 1995; Maeno et al. 2000a, b). In primary cultures of adult rat myocytes established under serum-free conditions and incubated 24 h with METH (0.01 and 1 mM), cellular granulation and swelling, myocyte hypercontraction, broken cellular membrane, and cellular destruction were observed under the light microscope. Under the same conditions of incubation, electron microscopy revealed swelling and irregular mitochondria with disrupted cristae, clump of sarcomeres with nearly complete loss of organized contractile elements, injury of intracellular membrane system, and dissolution of myofibrils (He 1995). In isolated adult rat ventricular cardiomyocytes incubated with METH (0.05, 0.1, and 0.5 mM) for 7 days, myocyte size varied and microtubular actin structures showed signs of injury (Maeno et al. 2000b). In another study, the incubation with METH (0.05 and 0.1 mM) for 7 days after a 6-day period of normal culture led to a larger cross-surface area of isolated adult rat ventricular cardiomyocytes with more abundant actin bundles, clearly showing signs of cellular hypertrophy development caused directly by METH (Maeno et al. 2000a). Also, the effects of METH on ionic currents were investigated in isolated rat

ventricular myocytes using the whole-cell patch clamp technique. Methamphetamine had inhibitory effects on transient outward potassium current, inward rectifying potassium current, and L-type calcium currents in ventricular myocytes (Liang et al. 2010). In cultured neonatal rat cardiomyocytes, incubation with 0.5 mM METH changed beating rate and altered calcium oscillation pattern via the L-type calcium channels, in a manner independent of any neurotransmitter (Sugimoto et al. 2009). These alterations may account for some of the possible electrophysiological mechanisms of cardiac damage caused by METH.

There is sufficient clinical and experimental evidence to suggest that METH can have adverse and potentially fatal effects on the cardiovascular system. The existing literature suggests that: (1) METH users are at elevated risk of cardiac pathology; (2) risk is not likely to be limited to METH acute use, because the chronic METH use is also associated with cardiomyopathy (Hong et al. 1991; Ito et al. 2009; Yeo et al. 2007); (3) the risk of cardiac pathology is higher among chronic METH users; (4) pre-existing cardiac pathology, due to METH use or other factors, increases the risk of an acute cardiac event; and (5) METH use is likely to exacerbate the risk of cardiac pathology from other causes and may therefore lead to premature mortality (Kaye et al. 2007).

The cellular, animal, and human autopsy studies, individual case reports, and case series suggest that METH exposure is potentially associated with structural and functional changes of myocytes, as well as clinical manifestations of cardiomyopathy and congestive heart failure, which are dependent on METH effects towards the catecholaminergic system and also on METH direct cardiotoxicity.

3,4-Methylenedioxymethamphetamine cardiotoxicity

MDMA was thought to be safe by recreational users and by psychotherapists who supported its use. MDMA was used therapeutically as it was believed to increase patient self-esteem and facilitate therapeutic communication. The oral administration of MDMA (doses ranging between 75–175 mg) produced acute sympathomimetic effects, such as increased heart rate and blood pressure and transient anxiety (Greer and Strassman 1985; Grinspoon and Bakalar 1986; Lester et al. 2000; Mas et al. 1999).

It was perhaps the article by Dowling and coworkers that started to question MDMA safety by reporting five deaths associated with the use of MDMA and MDEA (Dowling et al. 1987). It was concluded that MDMA or MDEA may have contributed to death of three patients by the induction of arrhythmias in individuals with underlying natural disease, thus highlighting the severity of their effects in the heart (Dowling et al. 1987). In fact, MDMA-

related fatal complications have been often secondary to cardiac abnormalities, massive neurological disturbances, and multiple organ failure (Connolly and O'Callaghan 1999; Hall and Henry 2006; Henry 1992; Liechti et al. 2005; McCann et al. 1996). Hue and colleagues described 2 lethal cases associated with MDMA use. One whole tablet of ecstasy in one case and a half tablet of ecstasy in another case led to a lethal outcome. Severe myocardial contraction band necrosis was observed in these 2 cases as revealed by the histopathology examination. Focal interstitial infiltration of lymphocytes and monocytes around myocardial lesions in the first case was also found. The results suggest that contraction band necrosis can be induced by ecstasy and can be potentially lethal (Hua et al. 2009). Other post-mortem studies confirmed these effects. In fact, a 39-year-old woman collapsed after oral intake of MDMA. After ingestion of the drug, she felt persistent discomfort in her anterior chest area and lost consciousness for a few minutes on the following morning. She was transported to a hospital and died 7 days after collapse. A serum sample obtained on admission revealed a MDMA concentration of 1.2 mg/L, but no evidence of any other drug including AMPH, METH, or other ring-substituted amphetamines, thus excluding the presence of other potentially cardiotoxic amphetamines (Sano et al. 2009). Microscopic examination at autopsy revealed striking changes in the heart, predominantly in the right ventricle, including small foci of myocyte necrosis with a surrounding macrophage inflammatory response, foci of fibrosis, and calcification accompanied by myocyte necrosis (Sano et al. 2009). These data in humans were confirmed in animal models. In rats, MDMA is well known to produce a range of effects on the cardiovascular function, either after single or binge administration, at doses ranging from 10 to 30 mg/Kg. MDMA promotes an enhancement of cutaneous vasoconstriction both in rats and rabbits (Blessing and Seaman 2003; Blessing et al. 2003; Fitzgerald and Reid 1994; Ootsuka et al. 2004). In male albino rats administrated with 20 mg/kg i.p. MDMA, myocardial contraction band necrosis was observed after 6 h. After 16 h, monocytes around the necrotic myocardial cells were observed, and within 24 h, this infiltrate became more widespread with an early removal of the necrotic material. Calcium deposits were observed within ventricular cardiomyocytes with intact nuclei and sarcomeres.

Single administration of MDMA can significantly produce oxidative stress, which may result in lipid peroxidation and disruption of calcium homeostasis (Cerretani et al. 2008). The depression in calcium regulatory mechanisms by ROS ultimately results in intracellular calcium overload, contraction band necrosis, and cell death. Also, the calcium involvement can favor arrhythmias.

In Sprague-Dawley rats, radiotelemetry was used to characterize the cardiovascular responses elicited during three MDMA binges (9 mg/kg, i.v., for 4 days), each binge separated by a 10-day MDMA-free period (Badon et al. 2002). The heart rate and mean arterial pressure responses elicited by 9 mg/kg doses of MDMA were consistent within and between the three binges (Badon et al. 2002). In the first binge, the 9 mg/kg doses of MDMA increased mean arterial pressure and produced a biphasic (decrease/increase) heart rate response. After repeated dosing, the pattern of mean arterial pressure and heart rate responses elicited by MDMA changed from that typically elicited by a sympathomimetic stimulant to one resembling vasovagal reflex activation (Badon et al. 2002). Over the course of several MDMA binges, there is an increased potential for MDMA to generate cardiac arrhythmias. In fact, in this study, MDMA produced cardiac arrhythmias in some rats. Finally, the binge administration of MDMA produced myocarditis. The hearts of MDMA-treated rats contained foci of inflammatory infiltrates (lymphocytes and macrophages), some of which contained necrotic cells and/or disrupted cytoarchitecture. The inflammatory infiltrate was predominantly lymphocytic with low content of monocytes. The degree of cardiac toxicity observed was proportional to the number of doses administered (Badon et al. 2002). These results indicate that binge administration of MDMA can significantly alter cardiovascular and cardiovascular reflex function and produce cardiac toxicity. This study corroborates the association between myocarditis and MDMA abuse observed in post-mortem studies conducted in MDMA users (Hua et al. 2009; Milroy et al. 1996).

It was shown in Sprague-Dawley rats that the effects of MDMA (9.19 mg/kg, i.p.) on the heart rate were dependent on the environmental temperature at which animals were kept during the drug administration. Rats kept at an elevated ambient temperature ($30 \pm 1^\circ\text{C}$) showed higher heart rate than animals exposed at room temperature ($21.5 \pm 1.5^\circ\text{C}$) (Jaehne et al. 2008). Furthermore, MDMA can produce a dose-dependent increase in mean arterial pressure and a range of other effects on the rat cardiovascular function, due to its cardiac stimulant effects, resulting in tachycardia and arrhythmia (Badon et al. 2002; Gordon et al. 1991; O'Cain et al. 2000). Importantly, in rats, MDMA and MDA, its main metabolite, produce a prolonged increase in both systolic and diastolic pressures, with MDA causing the most marked rise (Bexis and Docherty 2006).

In humans, the cardiovascular effects were evaluated in a double-blind, placebo-controlled trial in eight healthy adults who self-reported MDMA use. At a dose of 1.5 mg/kg MDMA, increased mean heart rate (by 28 beats/min), systolic blood pressure (by 25 mm Hg), diastolic blood pressure (by 7 mm Hg), and cardiac output (by 2 L/min) were observed. The effects of MDMA were similar to those of

dobutamine at 20 and 40 mg/kg per minute (Lester et al. 2000). However, in this study, MDMA showed no measurable inotropic effects. In the absence of inotropy positive response, incremental increases in afterload produce proportional increases in force or tension per unit of cross-sectional area of the ventricular wall. This increase in tension is known as wall stress and is directly related to myocardial oxygen demand. The dose-related increase in myocardial oxygen demand without an increase in contractility may lead to higher risk for cardiovascular complications in MDMA users (Lester et al. 2000). A randomized, double-blind, crossover, placebo-controlled trial was conducted in nine healthy male subjects (Farré et al. 2004). MDMA at a dose of 100 mg and the placebo were administered in two successive doses separated by an interval of 24 h. The second administration of MDMA slightly increased heart rate in comparison with the first administration, but the result was only significant 40 min after administration. Diagnostic criteria of isolated systolic hypertension (>140 mmHg) were met by six subjects following the first dose of MDMA and eight subjects following the second. Hypertensive episodes showed a mean duration of 1 h following the first dose and 1.4 h following the second dose. On the other hand, two subjects met diagnostic criteria of sinus tachycardia (>100 beats/min), both following the second dose of MDMA. Tachycardia lasted between 15 and 30 min (Farre et al. 2004). This work clearly demonstrates the hyperreactivity of the noradrenergic system in the cardiovascular system upon MDMA binge use.

MDMA, like other amphetamines, increases the endogenous and stimulated release of peripheral monoamines. MDMA causes the efflux of 5-HT and NA and to a lesser extent of DA by an exchange diffusion process involving the respective transmitter transport carriers (Capela et al. 2009). As stated, the acute administration of MDMA increases arterial pressure and heart rate in humans (Lester et al. 2000; Mas et al. 1999). In rats, the pressor responses elicited by MDMA involve the activation of α-adrenergic and serotonergic 5-HT₂-type receptors (McDaid and Docherty 2001).

MDMA has sympathomimetic actions in peripheral organs as demonstrated in vitro (Fitzgerald and Reid 1994) and in vivo (McDaid and Docherty 2001; O'Cain et al. 2000). Plasma concentrations of 5-HIAA, 5-HT, NA, adrenaline, and DA were determined in 159 ecstasy users and controls (Stuerenburg et al. 2002). "Ecstasy" users showed elevated sympathetic activity at rest, reflected in increased NA, adrenaline, and DA levels (Stuerenburg et al. 2002). Most surprising, in the drug-free interval, MDMA users showed elevated peripheral noradrenergic, dopaminergic, and adrenergic activities. These data could argue for a noradrenergic hyperreactivity in the drug-free interval in ecstasy users resulting from previous "ecstasy" consumption

(Stuerenburg et al. 2002). The catecholamine increase caused by MDMA consumption leads to sustained stimulation of adrenoceptors, which likely causes toxic effects, namely increased blood pressure, tachycardia, chest pain, myocardial ischemia, and cardiac arrhythmia (Costa et al. 2011). In fact, adrenergic stimulation is likely responsible for the formation of intracellular ROS within the first minutes. However, the cells have feedback mechanisms that change the adrenoceptors responsiveness. It is feasible that the oxidative stress induced by catecholamines hours after the initial exposure is, at least in part, due to the oxidation of those molecules (Costa et al. 2011). In vivo studies show that MDMA administration leads to oxidative stress. After administration of 20 mg/kg i.p. of MDMA to male albino rats, the activity of antioxidant enzymes in the heart was significantly reduced for GPX (by 24%) and SOD (by 50%) 3 h after and GR (by 19%) 6 h after treatment (Cerretani et al. 2008). The ascorbic acid levels decreased (by 37%) after 3 h and (by 30%) after 6 h, while malondialdehyde level increased (by 119%) after 3 h. GSH levels decreased after 3 h (by 31.3%) and 6 h (by 37.9%) after MDMA treatment (Cerretani et al. 2008).

In animal models, repeated administration of MDMA has resulted in myocarditis, contraction band necrosis, and fibrosis, most likely as a result of the noradrenergic properties of the drug (Badon et al. 2002; Cerretani et al. 2008; Sano et al. 2009). Recently, a new perspective upon MDMA-induced cardiotoxicity advocates that it could be caused (at least in part) by the metabolites of MDMA. Carvalho and coworkers demonstrated that incubation of isolated adult rat cardiomyocytes with metabolites of MDMA, N-Me-a-MeDA, and a-MeDA resulted in loss of normal cell morphology, which was preceded by loss of GSH, a sustained increase of intracellular calcium levels, ATP depletion, and a decrease in antioxidant enzyme activities (Carvalho et al. 2004c). Also, in adult rat left ventricular myocytes treated with MDMA, the production of ROS was not different from control, while all three metabolites of MDMA (a-MeDA, N-Me-a-MeDA, and 2,5-bis(glutathione-S-yl)-a-MeDA) exhibited time- and concentration-dependent increases in ROS that were prevented by the antioxidant NAC (Shenouda et al. 2009). Furthermore, the metabolites of MDMA, but not MDMA alone, significantly decreased contractility and impaired relaxation in myocytes stimulated at 1 Hz, being these effects also prevented by NAC (Shenouda et al. 2009). These *in vitro* studies suggest that MDMA-induced oxidative stress in the left ventricle can be due, at least in part, to the metabolism of MDMA to redox-active metabolites. Thus, MDMA-induced oxidative stress plays an important role in its cardiotoxic actions, being feasible that the redox-active metabolites of MDMA play an especially important part in MDMA-induced cardiac toxicity (Shenouda et al. 2010).

In summary, amphetamines are without doubt cardio-toxicants, as reported by several cellular and animal studies, but especially by human studies and case reports. The most obvious mechanism to their cardiac toxicity is their ability to activate the catecholaminergic system in the CNS and in the peripheral organs. This catecholaminergic activation can cause direct lesion on the heart or heart coronary system. In fact, several studies proved that also the direct action of amphetamines and/or their metabolites can trigger cardiotoxicity and that this direct cardiotoxic potential cannot be neglected in future studies.

Rhabdomyolysis and Kidney toxicity

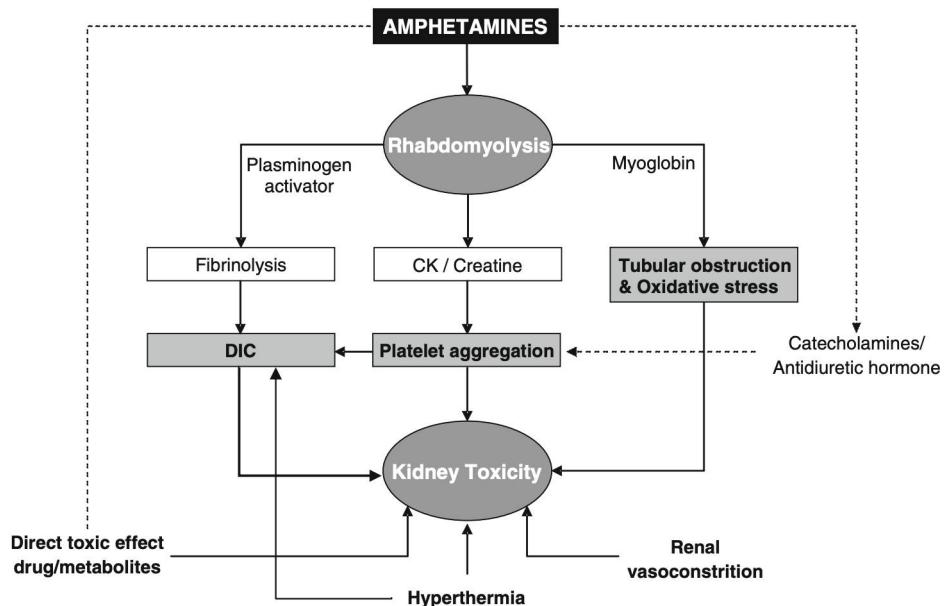
Rhabdomyolysis

Rhabdomyolysis associated with the use of AMPH and its methylenedioxymethamphetamine derivatives such as MDMA is commonly observed in young people after strenuous and exhausting muscle exercise in hot environments with virtually no ventilation (characteristic of rave parties) (Greene et al. 2003; Halachanova et al. 2001; Henry 1992; Ishigami et al. 2003; Murthy et al. 1997; Richards et al. 1999; Scream et al. 1992; Williams and Unwin 1997). Individuals with rhabdomyolysis typically have violent muscle pain, muscle weakness, and brown-colored urine.

Rhabdomyolysis is characterized by skeletal muscle injury with release of myoglobin and other intracellular proteins and electrolytes into the circulation (Bagley et al. 2007). There are numerous factors that can cause rhabdomyolysis. In the case of MDMA, and amphetamines in general, rhabdomyolysis seems to be caused by vigorous muscular exercise, hyperthermia, cellular hypermetabolism, reduced muscle perfusion, coagulopathy, and systemic hypotension (Kendrick et al. 1977; Terada et al. 1988). Histopathological analysis of muscle specimens from ecstasy consumers obtained *in vivo* or post-mortem revealed edema with inflammatory infiltrates, fibers in a hypercontracted state, and architectural disarray (Behan et al. 2000; Fineschi et al. 1999). Rhabdomyolysis often involves the myocardium (Scream et al. 1992). More recently, Duarte et al. (2005) showed enlargement of the interstitial space and presence of leukocyte infiltrates in the soleus muscle of mice administered with MDMA and submitted to exercise for 24 h (Duarte et al. 2005).

Breakdown of muscle cells results in the leakage of myoglobin, potassium, phosphorus, creatine, muscle enzymes, such as creatine kinase (CK) and alanine transaminase (ALT), and ADP (Bagley et al. 2007; Cunningham 1997; Williams and Unwin 1997). The release of K⁺ in heart muscle can lead to arrhythmias (Dhalla et al. 2001), and the release of CK, creatine, and probably ADP can

Fig. 6 Schematic representation of the proposed mechanisms involved in rhabdomyolysis and kidney toxicity induced by amphetaminic compounds



cause platelet aggregation (Kendrick et al. 1977). Also, the release of antidiuretic hormone (ADH or vasopressin) and catecholamines induced by MDMA may originate platelet aggregation (Filep and Rosenkranz 1987). In addition, the increased release of plasminogen activator from muscle and hyperthermia may cause excessive fibrinolysis (Chadwick et al. 1991; Terada et al. 1988). All these factors ultimately induce a state of DIC, which contributes to nephrotoxicity (Fig. 6). Kidney damage may appear following microvascular obstruction as a result of fibrin-platelet complexes formed inside the walls of blood vessels. In addition, myoglobin, which is filtered by the glomerulus, when in excess can lead to tubular obstruction and degeneration. Recent studies suggest that myoglobin can also cause renal damage via oxidative stress (Holt and Moore 2001; Ishigami et al. 2003).

Amphetamines nephrotoxicity

The first case of acute renal failure associated with AMPH ingestion was reported in 1970 by Ginsberg and coworkers (Ginsberg et al. 1970). Kendrick et al. (1977) later described five intravenous consumers of METH who developed DIC, rhabdomyolysis with myoglobinuria, and renal failure. Several cases of kidney damage secondary to the consumption of ecstasy were described thereafter, including acute or chronic renal failure (Bingham et al. 1998; Cunningham 1997; Fahal et al. 1992; Henry et al. 1992; Walubo and Seger 1999; Woodrow et al. 1995), necrotizing renal vasculopathy (Bingham et al. 1998), and acute transient proximal tubular injury (Kwon et al.

2003). Histopathological analysis performed in kidney biopsies from patients intoxicated with amphetamines (Bingham et al. 1998; Foley et al. 1984; Woodrow et al. 1995) and in fatal cases (Ago et al. 2006; Chadwick et al. 1991; Dar and McBrien 1996; Fineschi et al. 1999; Fineschi and Masti 1996; Ishigami et al. 2003) showed extensive tubular degeneration and necrosis, interstitial edema and hemorrhage, small vessel occlusion, infiltration of leukocytes in the renal medulla, and the presence of tubular casts showing anti-myoglobin immunostaining.

Mechanisms of amphetamines nephrotoxicity

Although there is undeniable evidence of the nephrotoxic effects of amphetamines, the mechanism responsible remains to be clarified. However, DIC and rhabdomyolysis are frequent clinical complications in amphetamines consumers, which can cause obstruction of the micro vasculature and tubular degeneration as a result of deposition of platelet aggregates or myoglobin, respectively (Cunningham 1997; Fahal et al. 1992; Fineschi and Masti 1996). This process can lead to sudden renal ischemia and eventually to acute tubular necrosis.

In addition, amphetamines have vasoconstrictive properties that predispose the renal medulla to ischemia and hypoxia. Finally, a possible direct toxic effect of the drug and/or its metabolites in the kidney was proposed by Foley and coworkers (1984) after observing a clinical case of acute interstitial nephritis in the absence of muscle damage and hyperpyrexia (Foley et al. 1984).

Hyperthermia

An overwhelming similarity observed in most cases of amphetamine-induced renal failure is the onset of hyperthermia. It has been shown that heat injury from any source can cause rhabdomyolysis, coagulopathy, and multiple organ failure (Dar and McBrien 1996). Therefore, it would seem reasonable to postulate that the hyperthermia induced by amphetamines is responsible for the ensuing renal damage especially when one observes the striking resemblance in the etiology of these cases to that of heatstroke (Chao et al. 1981; Lumertgul et al. 1992). Importantly, as previously mentioned, most cases involve young people who, after taking the drug, danced for hours in hot environments. Thus, the intense and exhausting muscular effort required in this type of parties associated with the high temperatures reached in the body are predisposing factors to the development of muscle and kidney damage.

Thioether toxicity

To our knowledge, neither AMPH nor METH have been proven to be directly nephrotoxic. Regarding MDMA, our group previously showed that neither MDMA nor MDA are directly toxic to either primary cultured rat or human proximal tubular epithelial cells (Carvalho et al. 2002b). In contrast, a-MeDA and the corresponding monoconjugate and biconjugate with GSH showed to be potent nephrotoxicants, thus indicating that metabolism is a prerequisite for the renal toxicity of MDMA. In addition, we showed the ability of acivicin, an inhibitor of γ -glutamyl transpeptidase (γ -GT), and bestatin, an inhibitor of aminopeptidase M, to potentiate the nephrotoxicity of 5-(glutathione-S-yl)-a-MeDA. These findings suggest that degradation of this conjugate by γ -GT and aminopeptidase M constitutes a detoxication mechanism. To explain this effect, it was hypothesized that γ -GT-mediated hydrolysis of 5-(glutathione-S-yl)-a-MeDA and subsequent aminopeptidase M-mediated glycine cleavage may lead to oxidative cyclization of the cysteine conjugate. In this reaction, the cysteinyl amino group condenses with the quinone carbonyl to give a benzothiazolyl-like compound. Since this reaction eliminates the reactive quinone function from the molecule, it effectively prevents redox cycling of the thioether. The intramolecular cyclization reaction can therefore be considered an intramolecular detoxication reaction. In addition, quinone thioethers are known to inhibit a variety of enzymes that utilize GSH as either a substrate or a co-substrate, including γ -GT (Monks and Lau 1998). Such an effect of the a-MeDA-GSH conjugate on γ -GT at PTC membranes may subsequently also increase extracellular concentrations of nephrotoxic metabolites of MDMA. Since these conjugates retain the ability to redox cycle, with the

concomitant generation of ROS, it is possible that they induce lipid peroxidation of cell membranes. In addition, GSH-linked α -quinones interact with thiol groups of extracellular functional proteins, which play a critical role in cell function. Thus, it seems that toxicity induced by thioether metabolites of MDMA at the apical membrane of renal proximal tubular cells is the result of extracellular events, presumably redox cycling.

In summary, it appears that conditions of enhanced oxidative stress in kidneys, in addition to hyperthermia, contribute to mechanisms of amphetamines-mediated nephrotoxicity. The risk of impaired renal performance increases if the developing hyperthermia is further aggravated by predisposing conditions such as high ambient temperatures, crowding, loud noise, alcohol/multi-drug use, inefficient fluid replacement, and elevated activity levels. However, one should always keep in mind that other factors such as genetic susceptibility and impurities in the street drugs may play a role in the observed toxicity.

Pharmacogenetics

The influence of genetic polymorphism on the metabolism and toxicity of amphetamines

Individual susceptibility to the adverse effects of any xenobiotic can be determined by the combination of (1) stable heritable traits occurring in the human genome, (2) non-genetic variables, and (3) gene-environment interactions. Therefore, genetic variation in genes coding the proteins involved in the drug kinetics and/or dynamics can be determinant for toxicity. Mutations in the genetic code may be responsible for differences in the subjective effects of drugs of abuse making them either more rewarding or aversive depending on the genotype (Haile et al. 2009). Some of these genetic polymorphisms affecting proteins that potentially contribute for amphetamines toxicity are discussed below.

Genetic polymorphism of metabolic enzymes

Several enzymes involved in the metabolism of amphetamines are functionally polymorphic, and their altered expression may therefore influence the pharmacokinetics of these drugs and in consequence their toxicity.

CYP2D6

CYP2D6 is the major enzyme involved in the oxidative metabolism of MDMA that in turn produces metabolites of recognized toxicity. Therefore, it was hypothesized that individuals carrying deficient alleles for the enzyme might

be at a higher risk for the occurrence of acute toxic effects (including hyperthermia and cardiovascular effects) resulting from a direct action of the drug (Greene et al. 2003; Segura et al. 2005). On the other hand, individuals carrying multiple copies of the CYP2D6 gene could be predisposed toward neurotoxicity due to the expected increased production of potentially neurotoxic metabolites (Segura et al. 2005).

The variation in MDMA metabolism and the consequent formation of the reactive catechol metabolites due to CYP2D6 deficiency were already evaluated in vitro (Ramamoorthy et al. 2002; Tucker et al. 1994) and in vivo in humans (de la Torre et al. 2005). One of these studies evaluated the metabolism of the drug in microsomes expressing the allele variants CYP2D6*2, *10 and *17 (Ramamoorthy et al. 2002). The CYP2D6*2 variant is associated with the intermediate metabolizer phenotype in Caucasians (Raimundo et al. 2000). The allele CYP2D6*10, highly prevalent in oriental populations, originates a deficiency in the tertiary and quaternary structure of the protein strongly impairing the expression of the functional enzyme (Johansson et al. 1994). The carriers of allele CYP2D6*17, highly prevalent in African populations, also exhibit diminished metabolic capacity (Masimirembwa et al. 1996). The microsomal preparations expressing variant CYP2D6*10 presented the lowest metabolic capacity for MDMA, followed by CYP2D6*2 and CYP2D6*17 (Ramamoorthy et al. 2002). The same authors had previously conducted a study comparing the catalytic activity of the variant enzyme CYP2D6*10 with wild-type CYP2D6*1 in MDMA demethylation and found that this metabolic reaction occurred to a much lesser extent with CYP2D6*10 than with CYP2D6*1 (Ramamoorthy et al. 2001). In this study, the authors also showed that both variants were inhibited by MDMA and that the *K_i* was significantly higher for variant CYP2D6*10 probably due to the lower affinity of the mutated enzyme toward MDMA (Ramamoorthy et al. 2001).

An in vitro study attempting to elucidate the influence of polymorphic expression of CYP2D6 on MDMA cytotoxicity used genetically modified V79 cells expressing the human wild-type CYP2D6*1, the low-activity alleles CYP2D6*2, *9, *10, and *17, and human CYP3A4 (Carmo et al. 2006). The results showed that the cytotoxic effects of MDMA were clearly increased in cells expressing CYP2D6*1 compared with the control cells devoid of CYP-dependent enzymatic activity. Toxicity in V79 CYP2D6*1 cells was also higher than in V79 cell lines expressing the low-activity alleles CYP2D6*2, *9, *10, or *17, whereas the CYP3A4 isoenzyme did not change MDMA toxicity. The formation of the N-Me-a-MeDA oxidative metabolite was greatly enhanced in the V79 cell line transfected with wild-type CYP2D6*1 compared to all other cell lines. The increase in the cytotoxic effects of MDMA observed in this cell line was therefore suspected

to be a consequence of the increased production of this reactive metabolite. The results confirmed this hypothesis as the metabolite proved to be more than 100-fold more toxic than the parent compound under the same experimental conditions (Carmo et al. 2006). In view of these data, it was speculated that CYP2D6 ultra-rapid metabolizers might be predisposed for MDMA intoxications due to the potential increase in toxic metabolite production (Carmo et al. 2006). In contrast, the susceptibility to the toxic effects of the drug that positively correlate with plasma concentrations would be expected to be lower in these individuals.

This study model was further used to elucidate the influence of polymorphic CYP2D6 expression on the cytotoxicity of another amphetamine derivative, 4-methylthioamphetamine (4-MTA, also known as the street drug flatliners) (Carmo et al. 2007). As with MDMA, the expression of wild-type CYP2D6*1 clearly enhanced the susceptibility to the cytotoxic effects of 4-MTA compared with the parental cells devoid of CYP-dependent enzymatic activity and the V79 cell lines expressing the low-activity alleles (Carmo et al. 2007).

The changes in MDMA pharmacokinetics associated with CYP2D6 deficiency were evaluated in vivo during a clinical study conducted with 10 healthy volunteers administrated with MDMA under controlled experimental settings (de la Torre et al. 2005). One of these individuals was homozygous for allele CYP2D6*4, which is associated with diminished enzyme activity, and 3 were heterozygous for alleles CYP2D6*1/4. The pharmacokinetic profile of MDMA and metabolites varied significantly according to the different CYP2D6 genotypes (Table 4) (de la Torre et al. 2005). It was observed that MDMA plasma concentrations were significantly higher in the individual with the poor metabolizer genotype, while the metabolite production was significantly lower. Also, for the extensive metabolizers, the time for maximal plasma concentration of the N-Me-a-MeDA metabolite was shorter, indicating that first-pass metabolism was likely impaired in the poor metabolizer. Heterozygous CYP2D6*1/*4 subjects presented intermediate pharmacokinetic parameters with statistically significant differences toward the extensive metabolizers and the poor metabolizer (de la Torre et al. 2005). Another interesting observation in this study was the higher increase in body temperature and the absence of MDMA-induced prolactin release in the poor metabolizer relative to the other 9 individuals. The authors suggested that these effects could be related with the phenotype, anticipating a higher risk for hyperthermia for the poor metabolizers (de la Torre et al. 2005). The observed pharmacokinetic differences could only be noted during the first 24 h after the first MDMA administration. After the second dose, and most likely as a result of CYP2D6

inhibition, differences among phenotypes were abolished (de la Torre et al. 2005).

In another study with the MDMA analogue MDEA, a lower production of the corresponding catechol metabolite after demethylation of the drug was observed in an individual homozygous for allele CYP2D6*4 (Kreth et al. 2000).

These data showing the influence of the different CYP2D6 genotypes on MDMA pharmacokinetics prompted the studies for the evaluation of the potential association between poor metabolizer phenotype and the occurrence of acute intoxication in recreational users.

The genotyping of 3 patients presenting severe MDMA-induced hepatotoxicity revealed that all were extensive metabolizers (Schwab et al. 1999). Similarly, two other studies in which individuals intoxicated with MDMA were genotyped also showed that the oxidative metabolism reduction was not associated with increased susceptibility to intoxication (Gilhooly and Daly 2002; O'Donohoe et al. 1998). Taken together, these data corroborate the speculation that phenotypes associated with higher metabolic capacity may predispose toward toxicity rather than be protective.

A recent study investigated the association of CYP2D6, COMT, and SERT genotypes with changes in cortisol plasma concentration following MDMA consumption in 48 subjects at a recreational setting (Wolff et al. 2011). Plasma cortisol concentrations increased after MDMA ingestion, and an association between CYP2D6 genotype and increase in cortisol levels was reported (Wolff et al. 2011).

Catechol-o-methyltransferase

In Caucasians, the frequencies for the phenotypes with distinct degrees of COMT enzymatic activity are 25% for the high-activity phenotype, 50% for the intermediate-activity phenotype, and 25% for the reduced-activity phenotype (Weinshilboum et al. 1999). These phenotypes have been attributed to a single-nucleotide polymorphism that changes amino acid valine with methionine at position 108 in soluble COMT and position 158 in membrane-bound COMT (Lachman et al. 1996; Lotta et al. 1995; Lundstrom et al. 1995).

The study of the influence of the val158met polymorphism on AMPH effects showed that individuals carrying the met/met genotype (homozygous for the mutation) seem to be at an increased risk for AMPH-induced adverse reactions (Mattay et al. 2003). Another study conducted with METH-dependent users found an association between this polymorphism and METH dependence (Li et al. 2004).

In the study conducted by Wolff and collaborators that evaluated the association of CYP2D6, COMT, and SERT genotypes with changes in plasma cortisol concentration

following MDMA consumption, a positive association between the low-activity COMT genotype (met/met) and MDMA-induced change in cortisol levels was found (Wolff et al. 2011).

Genetic polymorphism of pharmacological and toxicological drug targets

Proteins involved in the biological and toxicological actions of amphetamines can also be functionally polymorphic and, as such, associated with the marked interindividual variability in susceptibility toward the adverse effects elicited by these drugs of abuse.

These proteins include receptors, transporters, ion channels, lipoproteins, clotting factors, proteins involved in cell cycle control, in immune function, and in cellular development (Meisel et al. 2003).

Dopamine receptor

The polymorphism of D2 dopamine receptor was associated with increased vulnerability to psychostimulant abuse (Persico et al. 1996).

In a study attempting to associate the polymorphism of D4 dopamine receptors with METH abuse, an association between a haplotype in the promoter region of the gene coding for this receptor and a risk for METH dependence was found (Li et al. 2004). Another interesting result from this study that simultaneously analyzed the val158met COMT polymorphism was the finding of a significant interaction between this polymorphism and the polymorphism of D4 dopamine receptors, thus indicating a possible additive effect of both polymorphisms in risk for dependence of this drug of abuse (Li et al. 2004). Conflicting results were more recently reported in a study performed in patients with METH dependence and/or psychosis in a Japanese population (Ujike et al. 2009). In this later study, no significant association between polymorphism of DA receptors D2, D3, or D4 with METH dependence was observed. However, the data suggested that genetic variants of DA receptor D2, but not D3 or D4, increased individual risk for the rapid onset, prolonged duration, and spontaneous relapse of METH-induced psychosis (Ujike et al. 2009).

Serotonin transporter

The serotonin transporter is one of the initial targets of the amphetamines toxicological response. In humans, transcriptional activity of SERT gene (SLC6A4) is modulated by a polymorphic repetitive element (5HTT gene-linked polymorphic region, 5HTTLPR) located upstream of the transcription start site. Other sites for genetic variability

have been described, but this polymorphism seems to be the most important for SERT variability (Lesch and Gutknecht 2005). The majority of alleles are composed of either 14- or 16-repeat units (short and long allele, respectively), while alleles with 15-, 18- to 20-, or 22-repeat copies, and variants with single-base insertions/deletions or substitutions within individual repeats are rare. Allele and genotype distributions may vary considerably among different populations. The studies that characterized the influence of this polymorphism on the 5-HT uptake revealed that homozygous expression of the short allele is associated with a reduction in SERT expression and consequently with a lower 5-HT uptake ability (Lesch and Gutknecht 2005).

A study that evaluated the effects of the polymorphic expression of this transporter on the vulnerability toward the negative effects of MDMA on cognition associated with serotonergic function impairment indicated a likely association between this genetic variation and cognitive deficits induced by MDMA consumption (Roiser et al. 2006). A similar study conducted by the same research group had previously demonstrated that MDMA abusers homozygous for the SERT-mutated allele showed alterations in emotional processing in neuropsychological tests (Roiser et al. 2005). In contrast, individuals homozygous for this allele that did not consume MDMA did not show this disturbance. Based upon this data, the authors considered that there is a higher risk for the development of emotional dysfunctions in MDMA abusers who are carriers of the mutated allele, since these are more susceptible to the MDMA adverse effects on the serotonergic system (Roiser et al. 2005).

SERT genotype also seemed to influence the response to amphetamines effects as evaluated by a series of behavioral tests after controlled d-AMPH administration (Lott et al. 2006). A recent study provided evidence for the possible association between the SERT polymorphic expression and a greater risk for earlier onset METH use among METH-dependent Caucasian men (Johnson et al. 2010). A possible role for this polymorphism on METH-induced psychosis was also suggested in a study conducted with Japanese METH abusers (Ezaki et al. 2008). However, a previous study with a population of Chinese METH abusers failed to find such an association (Chen et al. 2007).

Other targets of amphetamines toxicological actions

The oxidative stress induced by METH in the brain has been implicated in its neurotoxic effects. The influence of the polymorphism of glutathione S-transferase M1 (GSTM1) on METH abuse was investigated since this enzyme is crucial for the detoxification of ROS. A possible

association between GSTM1 polymorphism and increased vulnerability to METH-induced psychosis was revealed in a Japanese population (Hashimoto et al. 2005).

The dopamine transporter (DAT) is also an important site for amphetamines action. A study on the effect of DAT1 polymorphism (coded by the SLC6A3 gene) revealed that the different genotypes were associated with different susceptibility to the subjective effects of d-AMPH administrated under the controlled experimental settings of a clinical study. This study showed that there is a possible influence of genetic variability of this transporter in susceptibility toward the psychostimulant effects and consequently on the risk for dependence of these type of drugs (Lott et al. 2005). A more recent study also evidenced increased sensitivity to the subjective effects of d-AMPH in individuals carrying the mutated genotype (Hamidovic et al. 2010). These genotypes were also associated with the risk for psychosis development in a population of METH abusers (Ujike et al. 2003).

The polymorphic expression of other proteins influencing response and/or dependence for amphetamines include the brain-derived neurotrophic factor (Flanagin et al. 2006; Sim et al. 2010), the opioid polypeptide prodynorphin (Nomura et al. 2006), the adenosine A_{2A} receptor that modulates the effects of dopaminergic receptors (Hohoff et al. 2005; Kobayashi et al. 2010), the GABA(A) receptor γ_2 subunit (Nishiyama et al. 2005), the norepinephrine transporter (Dlugos et al. 2009), and the μ -opioid receptor (Ide et al. 2006).

Factors affecting the stimulant/toxic effects of amphetamines

The type and/or severity of stimulant/toxic effects mediated by amphetamines are extremely unpredictable since they are determined by the conjunction of several factors including the dose and route of administration, the environmental conditions where amphetamines are consumed, the genetic, physiologic, and pathophysiologic characteristics of the consumer, and the co-exposure to other substances that can interact with these drugs. These factors can cause changes in the formation of active and/or toxic metabolites and, potentially, cause serious and even fatal intoxications.

Dose

The dose of amphetamines consumed will determine not only their addictive potential (Ellinwood and Kilbey 1980) but also the intensity and the persistence of their biologic and toxic effects, mainly due to the metabolic

auto-inhibition induced by these molecules (Kraemer and Maurer 2002). As with every illicit drug, both the dose and the purity of the amphetamines pills change substantially. This fact was observed in several studies concerning the analysis of the composition of ecstasy pills that showed variable doses of MDMA, but also other inert substances or psychoactive drugs (Baggott et al. 2000; EACD Expert Advisory Committee on Drugs 2004; Schifano et al. 1998; Spruit 2001; Tanner-Smith 2006) that can cause unexpected pharmacokinetic (PK) and/or pharmacodynamic (PD) interactions with unpredictable pathophysiological outcomes. In addition, tolerance is developed rapidly in amphetamines abuse (Leith and Barrett 1981). Therefore, periods of extended use require increasing amounts of the drug in order to achieve the same effect, which may potentiate the development of adverse effects.

Route of administration

There is some epidemiologic evidence reporting a relationship between the route of administration and the adverse effects of amphetamines (dependence symptoms, treatment-seeking, adverse psychological symptoms, and violence), independently of other risk factors, such as dosage and frequency of use. A higher prevalence of psychological symptoms, such as depression, anxiety, paranoia, hallucinations, and violence, was already related to the use of amphetamines by injection (Hall and Hando 1994).

Intravenous injection is the fastest route of drug administration, causing blood concentrations to rise the most quickly, followed by smoking, suppository (anal or vaginal insertion), insufflation (snorting), and ingestion (swallowing). Ingestion does not produce a rush which is most pronounced with the i.v. administration. On the other hand, intranasal administration of amphetamines results in a more rapid onset compared to oral dosing, which could be associated with the popularity of intranasal stimulant use and an enhanced potential for abuse (Lile et al. 2011).

Environmental conditions

The health-threatening risk associated with the consumption of psychoactive substances is also related to the environmental conditions surrounding the consumer (Bellis et al. 2002). In fact, the toxicity of amphetamines was shown to be potentiated under conditions of high environmental temperature (Miller and O'Callaghan 2003; Peterson and Hardinge 1967), repetitive high-volume noise (Gesi et al. 2002, 2004), stressful environments (Johnson et al. 2004), overcrowded places (aggregation effect) (Davis et al. 1974; Meyer et al. 2002b), intense physical activity (Parrott 2004, 2006), and inappropriately adjusted fluid intake (Cole and Sumnall 2003; Dafters 1995).

The environmental temperature can affect both the thermogenic effects of these compounds (Miller and O'Callaghan 2003; Peterson and Hardinge 1967), as well as their toxicokinetic profile by affecting their distribution volume (Banks et al. 2007) and their addictive potential (Banks et al. 2008).

Noise can increase the neurotoxicity of these compounds by increasing damage to dopaminergic terminals (Gesi et al. 2004) and can increase the risk of sudden death following rhabdomyolysis in the myocardium (Gesi et al. 2002).

Both stressful and overcrowded environments increase the acute effects of amphetamines as well as their addictive potential (Johnson et al. 2004; Meyer et al. 2002b).

Intense physical activity increases the toxicity of amphetamines (Parrott 2004) probably due to an increase in heat production, which contributes to the hyperthermic response.

Fluid intake can influence the toxicity of these compounds. While the absence of water consumption increases significantly the hyperthermic response (Dafters 1995), the exaggerated consumption of water can contribute to hyponatremia and consequent cerebral edema (Cole and Sumnall 2003).

Characteristics of the consumer

There are several consumer-inherent factors that can affect the risk associated with the consumption of amphetamines, since these factors determine his/her metabolic capacity, his/her susceptibility to develop acute effects, and also can influence the acquired consumption patterns. The main characteristics of the consumer which may influence the effects caused by amphetamines are as follows: age, ethnicity, gender, interindividual pharmacogenetic variations, sexual orientation, and physiologic and physiopathologic states.

Age

The consumption of amphetamines is mainly associated with younger age groups (United Nations Office on Drugs and Crime 2011). It is important to note that age can affect the expression of enzymes involved in the metabolism of these substances (Parkinson et al. 2004; Sotaniemi et al. 1997). Due to a higher metabolic rate of the enzymes involved in the metabolism of amphetamines (Parkinson et al. 2004), adolescents seem to have reduced sensitivity to the psychotropic effects of drugs like cocaine, ketamine, and MDMA, which can lead to a higher consumption per episode when compared with older individuals (Wiley et al. 2008). However, the latter, due to tolerance phenomena, are usually exposed to higher drug amounts per episode as

well as more amounts of other drugs to modulate the obtained effects (Scholey et al. 2004), therefore increasing the risk of interactions.

Ethnicity

Besides the influence of age, the consumption patterns of amphetamines are also influenced by ethnicity (Ompad et al. 2005). Genetic variation, as previously described, dietary, and lifestyle factors vary among different ethnic groups and may significantly modify the toxicological response to amphetamines.

Gender

Regarding the gender, women are more susceptible than men to the psychoactive effects and neurotoxicity of MDMA (Liechti et al. 2001; Parkinson et al. 2004), probably due to a lower metabolic capacity. However, men seem to be more prone to the hyperthermic effect and to the general toxicity of amphetamines (Miller and O'Callaghan 2003; Wyeth et al. 2009) probably due to their higher metabolic rate and consumption patterns (EMCDDA European Monitoring Centre for Drugs and Drug Addiction 2010), leading to higher formation of toxic metabolites.

Sexual orientation

The sexual orientation may affect the amount consumed and the frequency of consumption (Degenhardt 2005), conditioning the final outcome after consumption of amphetamines. In fact, lesbian/bisexual women usually consume larger amounts of drugs, namely MDMA, cocaine, METH, and LSD (Parsons et al. 2006), than heterosexual women. However, the frequency of consumption seems the same in both groups (Degenhardt 2005). With respect to men, the frequency of consumption of ecstasy has been shown to be higher in homosexual/bisexual than in heterosexual.

Physiologic and physiopathologic states

Besides the modulation of amphetamines response by the innate characteristics of the consumer, the acute and toxic effects caused by amphetamines can also be influenced by physiologic and physiopathologic states that can change the PK and PD of these drugs. We should highlight the influence of:

- Pregnancy—The use of psychoactive drugs by pregnant women has the potential to affect fetal development (McElhattan et al. 1999; Salisbury et al. 2009) and to increase the risk of hypertension-related complications.

Additionally, the mother can experience an increase in amphetamines neurotoxicity, due to the increase in CYP450 metabolism (Wadelius et al. 1997) and decrease in plasma protein binding (Notarianni 1990) that occurs during this period.

- Hypo/hyperthyroidism—Thyroid hormones (which are increased after amphetamines consumption (Mills et al. 2004)) are thermomodulators, and hyperthyroidism increases the hyperthermic effects of MDMA, while hypothyroidism does the reverse (Sprague et al. 2007).
- Kidney and liver failure—These pathologies imply a reduction in renal, hepatic, and intestinal clearance, modification of the distribution volume of the compounds, decrease in plasma protein binding, and decrease in tissue binding, altering the systemic bioavailability and increasing the risk for adverse reactions (Dreisbach and Lertora 2003; Kahraman et al. 2006), mainly of drugs with high first-passage metabolism.
- Inflammatory and infectious diseases—it is well established that inflammatory processes (Renton 2001) affect the metabolism, distribution, and elimination of certain drugs (Renton 2004). These effects result from the down-regulation of CYP450 and drug transporter proteins during the generation of host defense mechanisms. In clinical medicine, there are numerous examples indicating that a decrease in the capacity to handle drugs occurs during infections and disease states that involve an inflammatory component and that this decrease leads to the subsequent development of drug toxicity (Morgan 1997; Renton 2005).
- Cardiorespiratory disease—Amphetamines consumers who suffer from cardiorespiratory diseases will be less tolerant to amphetamines toxicity. In fact, fatal outcomes after amphetamines consumption seem to be more common in individuals with underlying cardiac disease (Chadwick et al. 1991; Dowling et al. 1987).
- Diabetes mellitus as well as obesity can alter the expression of metabolizing enzymes due to hormonal changes (e.g., insulin, glucagon, growth hormone, etc.) (Corcoran and Wong 1987; Kim and Novak 2007). The metabolic alterations can affect both the acute effects and the toxic profile of the amphetamines and can be further aggravated by the increase in oxidative stress phenomena that usually occur during these pathological states.
- Increase in corticosterone levels—The increase in corticosterone levels induced by amphetamines consumption (Nash et al. 1988), prolonged stress (Vallee et al. 1996), or chronic exposure to supraphysiological levels of corticosterone seems to increase the neurotoxicity of amphetamines, probably due to an increase in the vulnerability of the striatum, but not the hippocampus to S-(+)-MDMA neurotoxicity (Johnson et al. 2002a).

Co-exposure with other substances

Poly-consumption patterns can increase the health risks of amphetamines due to the unpredictable chemical and idiosyncratic reactions that can result from the mixture of xenobiotics in the body, potentially leading to PK and/or PD interactions.

Since, in humans, amphetamines are mainly metabolized by the enzymatic complex CYP450, their effects can be influenced by PK/PD interactions with other compounds (pharmaceuticals, drugs of abuse, nutrients, etc.) that share or affect the same metabolic pathway (Oesterheld et al. 2004). For example, CYP2D6 inhibitors including the protease inhibitor ritonavir, some selective serotonin re-uptake inhibitors, quinidine, imipramine, and thioridazine, may prolong amphetamine toxicity by reducing hepatic metabolism (de la Torre et al. 2004b). This postulate may also be applied to the potentiation, by amphetamines, of the deleterious effects mediated by drugs with narrow therapeutic windows that are CYP450 substrates (e.g., some tricyclic antidepressants, antiarrhythmic, β -blockers, antipsychotics, tramadol), since the metabolic auto-inhibition caused by the amphetamines can disproportionately increase the levels of the co-administered drug, leading to intoxication.

Being sympathomimetic, pro-serotonergic, and pro-dopaminergic drugs, amphetamines can potentially establish PD/toxicodynamic interactions with compounds that share the same mechanism of action or an antagonistic one (Oesterheld et al. 2004). In fact, the effects of the amphetamines might be potentiated by cocaine, anticholinergics, tricyclic antidepressants, theophylline, selective serotonin reuptake inhibitors (SSRI), monoamine oxidase inhibitors (MAOI), caffeine, salicylates, and LSD (Greene et al. 2008).

Some compounds can combine the two above-mentioned characteristics and simultaneously be pro-serotonergic/adrenergic/-dopaminergic, and CYP450 inhibitors, potentially causing unpredictable PK and PD interactions with amphetamines (Oesterheld et al. 2004). For example, fluoxetine, paroxetine, and cocaine are both selective inhibitors of 5-HT reuptake and potent CYP450 2D6 inhibitors, increasing both the concentration of MDMA (PK interaction) and the serotonergic activity (PD interaction) (Ramamoorthy et al. 2002).

The co-exposure to amphetamines and other compounds may be related not only with the common poly-consumption of other licit and illicit substances along with amphetamines, but also with the exposure to psychoactive substances inadvertently ingested as contaminants of amphetamine pills (Baggott et al. 2000) as well as with the consumption of pharmaceuticals (as part of medical treatments or to intentionally modulate the effects of amphetamines).

Pills contaminants

Club drug pills are very heterogeneous and variable in terms of their ingredients (Cole and Sumnall 2003). In fact, they can contain only inert substances (sodium bicarbonate, talc, sugars), different percentages of amphetamines, a totally different drug than the one that the consumer intends to buy, or the desired drugs might be mixed with other contaminants (Giroud et al. 1997). For example, METH is often mixed or “cut” with other substances, including caffeine or talc, to add bulk, improving profit margin (Greene et al. 2008). Due to these contaminants, the toxic effects of the amphetamines may only be part of the potentially lethal effects that may arise from the consumption of these pills. Some of the contaminants may be safe, but others might cause devastating, acute, or long-term effects. Other problem with the decrease in the purity of amphetamines pills is that while the amphetamines content decreases, the user tends to increase the number of pills consumed to obtain the desired effects (Schifano 2004), which increases the risk of toxic effects caused by the contaminants in the pills, or of an overdose if a sample with higher purity is taken in sequence.

Among the contaminants in amphetamines pills, we may expect to find: by-products of chemical synthesis, amphetamines mixtures, ketamine, ephedrine and derivatives, caffeine, LSD, dextromethorphan, and inert excipients. Although we may think that the inert excipients present in amphetamines pills cannot affect their effects, the fact is that the inclusion of sodium bicarbonate in these pills is made with the intention of prolonging their effects through the alkalinization of the excretion fluids, which will delay the elimination of the amphetamines.

By-products of chemical synthesis

Although there is no analytical evidence showing the presence of by-products of chemical synthesis in all the batches of amphetamines pills, their eventual presence is of high concern, since some of these compounds, namely MDA, saphrol and analogues, tetrahydrofuran, methanol, and N-methylformamide, among others (Shulgin 1986), may interact with MDMA effects, and, more importantly, they may also have intrinsic serious toxic profiles that can increase the risk of a health-threatening outcome after amphetamines pills consumption.

Amphetamines mixtures

Amphetamines pills rarely contain only one type of these stimulants and are most often constituted by amphetamines mixtures. In fact, it is usual to find MDMA in association

with MDA, MDEA, METH, or others. Because they share metabolic pathways and mechanisms of action, the interaction potential is very high, and they can cause additive reactions, increasing the deleterious effects exerted by each individual compound. For example, the co-consumption of MDA, AMPH, MDMA, and PMA was already associated with lethal intoxications (Dams et al. 2003), and the same was also observed with simultaneous exposure to MDEA and MDMA (Fineschi and Masti 1996). It was also demonstrated that the combination of MDMA with METH causes synergistic euphoric and pro-social effects (Clemens et al. 2007) and stronger toxic reactions than each one of the drugs, separately (Clemens et al. 2004). In addition, all the phenylisopropylaminic amphetamines are CYP inhibitors, which will increase the plasma levels of amphetamines, and therefore increase the risk of acute toxicity. It is also important to stress that if the relative proportion of pro-dopaminergic amphetamines in the pills is higher, the addictive potential of these pills will be increased (Garcia-Rates et al. 2007).

Caffeine

Exposure to caffeine occurs not only with the contamination of pills but also with the consumption of coffee, cola sodas, or energetic drinks that are often consumed to decrease tiredness and sleepiness. This xanthine, when co-consumed with MDMA, increases the MDMA-induced DA release (Vanattou-Saifoudine et al. 2011), potentiates its serotonergic neurotoxicity, increases the intensity and duration of the MDMA-related hyperthermic response (Vanattou-Saifoudine et al. 2010a; Vanattou-Saifoudine et al. 2010b), induces a persistent profound tachycardia, not seen when both compounds are consumed separately, and increases the weight loss caused by neurotoxic doses of MDMA, probably due to synergistic anorectic effects (Camarasa et al. 2006; McNamara et al. 2006). It was also already shown that caffeine induces convulsive states when administered with MDA and also increases the intensity and duration of the MDA-related hyperthermic response and decreases the brain levels of 5-HT and its metabolites (McNamara et al. 2006). Caffeine seems also to affect the PK of the amphetamines by increasing their intestinal absorption (Kuwayama et al. 2007). Probably due to a confluence of the above-mentioned phenomena, caffeine was already proved to increase mortality after acute co-administration of AMPH, MDMA, and MDA (Derlet et al. 1992). Therefore, while caffeine is considered safe and freely accessible in drinks like tea, coffee, and non-alcoholic beverages, its ingestion with amphetamines can exacerbate their toxicity, increasing the health risk associated with the consumption of these drugs.

Dextromethorphan

The presence of the antitussive dextromethorphan is very common in stimulant pills, and, due to its mechanism of action, dextromethorphan can potentiate the pro-serotonergic effects of the amphetamines (Kamei et al. 1992). In addition, since both compounds are metabolized through the CYP450 system, they may compete for the metabolic pathways, increasing the incidence and severity of the adverse effects of both substances. However, until now, there was no report on intoxications of this nature (de la Torre et al. 2004a).

Intentional poly-consumption of recreational drugs

Intentional poly-consumption of recreational drugs is the most frequent behavior pattern of amphetamines consumers, with high prevalence of co-consumption of other psychoactive substances especially tobacco, cannabis, and alcohol, and also other amphetamines, cocaine, LSD, ketamine, GHB, psilocybin/psilocin, and heroin. It was already described that the intensity and the pattern of use of amphetamines will alter the propensity of the individuals for drug poly-consumption (Scholey et al. 2004). These other substances might be consumed before, during, or in a short period after exposure to amphetamines (EACD Expert Advisory Committee on Drugs 2004). The need of drug poly-consumption may arise as a consequence of PD tolerance appearing after regular consumption of amphetamines, in an attempt to obtaining pleasant experiences (Parrott 2001), but also of decreasing the withdrawal symptoms. In fact, ethanol, benzodiazepines (Copeland et al. 2006), cannabis (Sala and Braida 2005), sildenafil (Breslau 2002), anti-histaminics (Winstock et al. 2001), and 5-hydroxytryptophane (Copeland et al. 2006) are usually taken to decrease the undesired effects of amphetamines. Therefore, this poly-consumption hampers the assessment of the long-term effects of amphetamines by masking them with the effects of the co-consumed psychoactive drugs (Cole and Sumnall 2003).

In addition, the simultaneous use of multiple psychostimulant drugs increases not only the risk of problems related with sympathomimetic over-stimulation [e.g., dehydration, hyperthermia (Williams et al. 1998), and cardiovascular problems (Milroy et al. 1996)] but also the chances to develop neurotoxicity (Winstock et al. 2001). For example, the poly-consumption patterns that include MDMA were already associated with impairments in set shifting and memory updating and also in social and emotional judgement processes (Reay et al. 2006). Also a case of amnesia syndrome and severe ataxia was described following the co-consumption of MDMA, together with amyl nitrate, lysergic acid (LSD), cannabis, and ethanol (Kopelman et al. 2001).

Cannabis

The majority of the amphetamines consumers also consume cannabis (Parrott et al. 2007). The consumers of amphetamines use the relaxing properties of cannabis and its derivatives to reduce the typical symptoms of anhedonia and depression that appear in the days subsequent to amphetamines consumption (Parrott and Lasky 1998). However, cannabis contributes to psychological problems, cognitive deficiencies, and other neurobiological problems (sleep disorders, sexual dysfunction, reduced immunocompetence, endocrine disorders, and oxidative stress) (Parrott 2006) in MDMA users, which can be cumulative at the long term, especially impulsivity, anxiety, obsessive-compulsive patterns, psychotic behaviors, as well as neuropsychological deficits (memory, learning, word fluency, and speed of processing) (Dafters et al. 2004). In fact, when the main active metabolite of cannabis, A⁹-tetrahydrocannabinol (THC), is administered simultaneously with MDMA, there is a synergistic disruption of memory in rats (Young et al. 2005), and a low dose of THC can modulate the sensitivity of animals to the behavioral effects of MDMA (Robledo et al. 2007). This interaction can be due, at least in part, to the fact that THC and MDMA converge at a common mechanism modulating dopamine outflow in the nucleus accumbens of mice (Robledo et al. 2007). Furthermore, the co-exposure to amphetamines and cannabis, especially at the long term, cause changes in the immunological homeostasis, with a decrease in the total number of lymphocytes, that may result in the increased susceptibility to infections and in immunological diseases (Pacifici et al. 2007). The combined intake of MDMA and THC also affects ongoing electroencephalogram oscillations differently than the sum of either one drug alone. Concretely, combined intake of MDMA and THC affects theta and lower-1 alpha power less than the sum of the single-drug effects, but exacerbates the reductions in lower-2 alpha power, which may be related to the impaired task performance that has often been reported after drug intake (Lansbergen et al. 2011). On the other hand, cannabinoids can prevent the acute hyperthermia and decrease the 5-HT depleting effects of MDMA, and, therefore, partially protect against MDMA neurotoxicity in rats (Morley et al. 2004). We can also expect to have some PK interaction between amphetamines and cannabis since THC and its derivatives are metabolized through the CYP450 complex (Matsunaga et al. 2000).

Cocaine

Cocaine is often used to potentiate the psychostimulant effects of amphetamines by increasing the synaptic levels of DA, 5-HT, and NA, although it also increases their dopaminergic

neurotoxicity (Daza-Losada et al. 2008). Cocaine effects may be also modulated by amphetamines. The repeated pre-exposure of rats to MDMA increased the locomotor activity and the addictive effects induced by cocaine (Fletcher et al. 2001). Another PD interaction of cocaine and amphetamines may arise from the fact that both drugs induce hyperthermia in an extent dependent on the environmental temperature (Gonzalez 1993). In addition, cocaine is also a CYP2D6 inhibitor, reducing the metabolism of amphetamines and increasing their blood levels (Shen et al. 2007).

Ketamine and ephedrine

Ketamine and ephedrine, like amphetamines, also have thermogenic, sympathomimetic, and pro-dopaminergic effects that may cause PD interactions with amphetamines and increase their addictive potential (Soni et al. 2004; Wolff and Winstock 2006). Besides the possible PD interactions, ketamine and ephedrine may also affect the PK of amphetamines by competing for the same metabolic pathways (Hijazi and Boulieu 2002; Soni et al. 2004), but also by decreasing the intestinal absorption of amphetamines (Kuwayama et al. 2007).

Furthermore, ketamine can affect the toxicity of amphetamines by causing amnesia that may increase the number of pills consumed per episode, increasing the probability for overdose and intoxication. The risk of cardiac over-stimulation is one of the potentially lethal consequences of combining ketamine with amphetamines (Gill and Stajic 2000).

LSD

The co-consumption of LSD (a strong hallucinogenic) and amphetamines (known as candyflipping or XL) is increasing, and it results in a synergistic pro-serotonergic interaction that may also increase their toxic response (Schechter 1998). Although PK interactions with amphetamines were not yet reported, an important role for CYP450 2D6 (CYP2D6) in the metabolism of LSD has been revealed by some studies (Yu 2008), suggesting that the co-consumption of amphetamines and LSD could act additively at the kinetic and dynamic levels, leading to severe or even fatal serotonin toxicity.

GHB

The co-consumption of amphetamines and γ-hydroxybutyric acid (GHB, liquid ecstasy) can result in different kinds of PD interactions. This co-consumption attenuates the dysforic unpleasant effects of amphetamines (due to the GHB effects at the central dopaminergic system) (Uys and Niesink 2005) and causes long-lasting neuroadaptations in

brain oxytocin system that may be related to the long-term social interaction deficiencies caused by both drugs (van Nieuwenhuijzen et al. 2010). On the other hand, GHB reduced the hyperthermia and hyperactivity produced by co-administered doses of MDMA or METH at 28°C (van Nieuwenhuijzen and McGregor 2009).

The establishment of PK interactions between GHB and amphetamines seems improbable since these drugs do not share metabolic pathways.

Psilocybin/psilocin

The consumption of "Magic" mushrooms containing psilocybin/psilocin along with amphetamines has a great potential for the establishment of PD interactions, since psilocybin/psilocin have sympathomimetic pro-serotonergic and pro-dopaminergic effects (Passie et al. 2002).

Tobacco

Tobacco is extensively consumed among amphetamines users, and it has a strong potential to establish PK interactions with these drugs, since some of its constituents (nicotine, polycyclic aromatic hydrocarbons, and other combustion products) are potent CYP450 and UGT inducers (Benowitz 2008). Furthermore, the activation of nicotinic receptors by tobacco nicotine will release DA, NA, acetylcholine, 5-HT, GABA, glutamate, and endorphins (Benowitz 2008), which may cause PD interactions with amphetamines.

Ethanol

Ethanol is one of the substances more frequently consumed with amphetamines. Combined use of MDMA and alcohol causes dissociation between subjective and objective sedation, which makes subjects feel euphoric, less sedated, and having the feeling of doing better, but actual performance ability continues to be impaired by the effect of alcohol (Hernandez-Lopez et al. 2002). MDMA moderated the impairing effects of a low dose of alcohol on road-tracking performance, but it could not overcome alcohol-induced impairment on other aspects of driving behavior or driving-related performance (Kuypers et al. 2006). Ethanol seems also to increase the risk of appearance of psychopathological disorders associated to MDMA consumption, since those who consumed alcohol together with MDMA had a risk 2.5 times higher, with respect to alcohol abstainers, of eventual development of psychopathological disturbances (Schifano et al. 1998). A collateral risk associated with the co-consumption of amphetamines and ethanol is the spread of sexually transmitted diseases due to an increase of sexual risk behaviors (Breen et al. 2006).

When co-consumed with amphetamines, ethanol can cause important PD interactions and slight PK interactions (de la Torre et al. 2004a). Ethanol can establish PD interactions with amphetamines that may be antagonistic (due to its pro-GABAergic activity) as well as additive or synergistic effects (pro-serotonergic and pro-dopaminergic stimulations; muscle damage and neuroendocrine, cardiovascular, hepatotoxic, nephrotoxic, and teratogenic effects). The most relevant PD interactions between ethanol and amphetamines are the thermoregulatory changes and the psychomotor and immunological effects. In fact, ethanol co-administered with MDMA at normal ambient temperature increases dramatically the MDMA-induced hyperlocomotion and decreases the MDMA-induced hyperthermic response (Hamida et al. 2008). The extent of this effect is increased with subsequent administrations of ethanol and depends on MDMA dose (Hamida et al. 2008) and on ambient temperature (Cassel et al. 2007), since prevention of MDMA-induced hyperthermia by ethanol was not observed when both compounds were administered at high environment temperature (32°C). These psychomotor and thermoregulatory effects are thought to be caused by the potentiation caused by ethanol on the MDMA-induced 5-HT and DA release at the striatum (Riegert et al. 2008). Furthermore, as it was already described for cannabis, the combination of MDMA and ethanol causes a transient defect in immunological homeostasis characterized by a higher suppressive effect on CD4 T cells and increasing effect in NK cells than any of the drugs alone and a deregulation in the production of pro- and anti-inflammatory cytokines with an unbalance toward anti-inflammatory response that might alter the immune response with a risk for the general health status (Pacifici et al. 2001). In addition, the co-exposure to ethanol and MDMA enhanced MDMA-mediated long-term neurotoxicity in rats (Izco et al. 2007) as well as its hepatotoxicity in vivo and in vitro on primary cultured rat hepatocytes (Pontes et al. 2008a). The PK interactions may arise from the different dose-dependent effects of ethanol on several CYP450 isoenzymes (Busby et al. 1999). In fact, ethanol increases MDMA levels in the striatum and prevents the MDMA-induced DA depletion and inhibition of tyrosine hydroxylase in mice (Johnson et al. 2004). The increase in MDMA levels in the presence of ethanol was also observed in humans (Hernandez-Lopez et al. 2002; Ramaekers and Kuypers 2006), which indicates the possibility of a PK interaction between these substances. However, the effects of ethanol on MDMA metabolism are controversial, because in some studies, ethanol decreased the metabolism of MDMA to MDA (Ben Hamida et al. 2007), in others, ethanol exposure increased the metabolism of MDMA to HMA and MDA in a temperature-dependent fashion, in a pathway mediated, at least partially, by CYP3A and

CYP2E1 (Pontes et al. 2010). Probably due to the metabolic interaction between these two compounds, some amphetamines users refer that ethanol blocks or counteracts the pleasant effects of MDMA and increases its collateral effects and vomiting (Solowij et al. 1992).

Heroin

Other drugs such as heroin seem also to increase the toxicity of amphetamines, although the underlying mechanism is not elucidated yet (Gerevich 2005).

Amphetamines mixtures

Finally, synergic toxic effects may appear, and the long-lasting deleterious effects may be prolonged when co-consuming different amphetamines that will increase neurotoxicity, probably by an increase in oxidative aggression (Gouzoulis-Mayfrank and Daumann 2006). The simultaneous consumption of MDMA and METH seems to be particularly dangerous (Clemens et al. 2007). However, MDMA seems to reduce the positive reinforcement effects of METH (Clemens et al. 2006). Fatal intoxications associated with simultaneous consumption of MDMA, AMPH, MDA, and PMA were already described, being characterized by disseminated intravascular coagulation induced by hyperthermia (Dams et al. 2003). And, obviously, PK interactions are also expected due to the common metabolic pathways of these compounds. In fact, pre-exposure to MDA inhibits MDMA metabolism, increasing the brain levels of the latter (Hashimoto et al. 1993).

Intentional poly-consumption of medications

Some medications and food supplements are intentionally used after amphetamines consumption to modulate their unpleasant effects (Copeland et al. 2006). The most common medications intentionally consumed with amphetamines are benzodiazepines and sildenafil, followed by antidepressants. The nutritional supplement most commonly consumed is 5-hydroxytryptophane (Copeland et al. 2006).

Antidepressants

Antidepressants, like amphetamines, increase the amount of neurotransmitters in the synaptic cleft, and they are used by ecstasy consumers to prevent eventual neurotoxic effects, to avoid the negative effects associated with the abstinence of this drug, to increase the intensity of its effects, to prolong the duration of the effects, or to facilitate sleep (Copeland et al. 2006). Some amphetamines, such as PMA, do not require an antidepressant for these

purposes because they are themselves MAO_i (Freezer et al. 2005). The most commonly used antidepressants are the SSRI (e.g., citalopram, fluoxetine, paroxetine, sertraline), the MAO_i (e.g., phenelzine, moclobemide), and the noradrenaline reuptake inhibitors (e.g., desipramine).

Although some antidepressant medications may block the subjective and some cardiovascular effects of amphetamines, they do not prevent the hyperthermic response (Liechti et al. 2000a; Stanley et al. 2007; Tancer and Johanson 2007) and can increase the risk of the onset of a serotonergic syndrome. In fact, SSRI decrease MDMA-induced 5-HT release, attenuate its behavioral effects in animals (Meehan et al. 2002), and reduce the subjective and cardiovascular response in humans (Liechti et al. 2000a; Tancer and Johanson 2007). However, the blood pressure response to MDMA is only partly attenuated by blockade of 5-HT release with citalopram (Liechti and Vollenweider 2000). The NAT inhibitor desipramine and the SERT inhibitor citalopram, but not the DAT/NAT inhibitor methylphenidate, reverse the acute cognitive effects of MDMA in rhesus monkeys (Verrico et al. 2008). However, the DAT/NAT inhibitor bupropion was shown to attenuate subjective responses to METH (Newton et al. 2006). Overall, the NAT inhibitors (e.g., nisoxetine, atomoxetine, reboxetine) cause a pronounced decrease in the cardiovascular stimulant effects of amphetamines (Hysek et al. 2011; Quinn et al. 2006; Sofuoğlu et al. 2009) and a moderate attenuation of their psychostimulant properties (Hysek et al. 2011; Sofuoğlu et al. 2009), despite inhibiting their metabolism (Hysek et al. 2011).

Despite some MAO_i being used by amphetamines consumers to “increase the peak”, frequent fatal outcomes due to the potentiation of the pro-serotonergic effects of this association have been reported (Pilgrim et al. 2010, 2011, 2012; Vuori et al. 2003), mainly related to the consumption of amphetamines along with MAO-A inhibitors (e.g., moclobemide, clorgyline). Contrary to what is observed with MAO-A inhibitors, the selective MAO-B inhibitors (e.g., selegiline, L-deprenyl) seem to confer some protection against MDMA neurotoxicity by decreasing the depletion of 5-HT in the brain, the formation of reactive species resulting from MAO-B action on the released catecholamines, and therefore the lipid peroxidation and the oxidative damage to the mitochondria (Alves et al. 2007, 2009; Sprague and Nichols 1995).

Furthermore, some antidepressants (e.g., fluoxetine, paroxetine) can inhibit CYP450 causing simultaneously PD (through their pro-serotonergic action) and PK (through the increase of MDMA plasma levels due to the inhibition of its metabolism) interactions (Ramamoorthy et al. 2002). Therefore, these compounds may decrease the neurotoxicity of MDMA metabolites (Sanchez et al. 2001), but they cannot prevent the acute effects of the amphetamines

because their levels will be higher for longer periods (Upreti and Eddington 2008).

Benzodiazepines

Benzodiazepines, by facilitating GABA receptor-mediated CNS inhibition, are indirect antagonists of amphetamines sympathomimetic effects (Derlet et al. 1990; Nisijima et al. 2003), and therefore are the first-line agents to control these symptoms of amphetamines intoxications at emergency departments. However, it should be highlighted that the AMPH-induced hyperactivity is potentiated by the benzodiazepine chlordiazepoxide, resulting in heightened levels of hyperactivity relative to levels triggered by either compound alone. This interaction effects of the AMPH-chlordiazepoxide combination are not explained by a PK interaction as both drugs have similar brain and plasma exposures, either administered alone or in combination, but combining chlordiazepoxide with AMPH results in an inverted-U dose-response (Kelly et al. 2009).

Anabolizant androgenic steroids

Also the pre-exposure to anabolizant androgenic steroids (e.g., nandrolone) can modulate the behavioral and compensatory effects of amphetamines in a dose-dependent manner, decreasing amphetamines effects at low doses (Kurling et al. 2008).

Possible interactions with therapeutic drugs regimens

The most prevalent interactions of amphetamines with medications appear in cases of association of amphetamines with antidepressants and anti-retro virals. However, several medications can inhibit the isoenzymes involved in amphetamines metabolism (Parkinson et al. 2004) or interact with the same receptors, transporters, or neurotransmitters. Some examples are haloperidol (Liechti et al. 2000a), clozapine, olanzapine (Blessing et al. 2003), barbiturates (Davidson et al. 2001), and acetylsalicylic acid (Davidson et al. 2001).

Some antipsychotics, including droperidol, haloperidol, olanzapine, and pimozide (DA D₂ receptors antagonists), can also reduce amphetamines-induced euphoria (Brauer and De Wit 1997; Liechti et al. 2000a) and lower seizure threshold, induce hypotension and dysrhythmias, but will impair heat dissipation (Whelan et al. 2004), which in turn increases amphetamines toxicity. On the other hand, chlorpromazine (a typical antipsychotic) and the 5-HT_{2a} antagonist cyproheptadine appear efficacious in treating 5-HT toxicity (Nisijima et al. 2001).

The sympathomimetic medications prescribed to treat some pathologies (e.g., fluoxetine, St. John's worth,

tramadol, venlafaxine, lithium, clomipramine, MAOIs (Smilkstein et al. 1987), tricyclic antidepressants, etc.) can increase the risk and the severity of the pro-serotonergic/-adrenergic/-dopaminergic effects caused by amphetamines consumption. However, the long-term exposure to the antidepressant fluoxetine seems to have beneficial effects regarding the long-term unpleasant effects posterior to amphetamines consumption (Thompson et al. 2004a). In addition, MAOIs (Smilkstein et al. 1987) and tricyclic antidepressants also increase amphetamines effects by slowing down CYP450 metabolism.

Some myorelaxants (e.g., succinylcholine) and some anesthetics (e.g., halothane) can cause malignant hyperthermia in predisposed individuals (Klein and Kramer 2004).

The exposure to the anti-hypertensive drug ketanserine reduces the perceptive effects of amphetamines (Liechti et al. 2000b), although other antihypertensives such as β -blockers can cause serious interactions with amphetamines, since blockade of β_2 -receptors (mediating skeletal muscle vasodilation) can produce unopposed α -receptor stimulation and uncontrolled hypertension (Hall and Henry 2006).

Adrenergic α -receptor (e.g., carvedilol) and α -receptor antagonists can reduce MDMA-induced hyperthermia in rats (Sprague et al. 2005). The α -receptor antagonist prazosin was also able to reverse MDMA-associated locomotor stimulation (Selken and Nichols 2007) and vascular effects (McDaid and Docherty 2001) in rats.

The anti-retrovirals such as ritonavir have been commonly involved in potentially lethal interactions with amphetamines (Antoniou and Tseng 2002). These drugs can strongly interact with a large number of compounds because most of them are substrates and potent inhibitors of the CYP450 system (Antoniou and Tseng 2002) and were already associated with some severe or even fatal interactions with amphetamines (Harrington et al. 1999; Henry and Hill 1998).

The opiate antagonist, naltrexone, currently used as a pharmacotherapy for alcohol dependence, attenuates the subjective effects induced by AMPH in humans (Jayaram-Lindstrom et al. 2008; Jayaram-Lindstrom et al. 2004) and reduces craving and the propensity to relapse to drug use in AMPH-dependent patients. In addition, several experimental studies show that both naltrexone and the opiate receptor antagonist naloxone reduce amphetamine-induced locomotor activity in several species and attenuate the threshold currents for self-stimulation by AMPH in rats and attenuate locomotor behavior in amphetamine-conditioned animals (Haggkvist et al. 2011).

Possible interactions with food

Food and food supplements ingested by amphetamines consumers may affect amphetamines effects by establishing PD

and PK interactions. For example, Ephedra supplements, used for weight loss, cause sympathomimetic effects that may potentiate the acute effects of amphetamines and cause potentially lethal complications (Chen et al. 2004). Some other compounds can PD interact with amphetamines because they are MAO_i (e.g., coumarin, flavones, xantones, etc.) (Thull and Testa 1994). Also the polycyclic aromatic hydrocarbons (PAHs) present in charcoal-grilled food are known to induce the CYP450 system (Felton and Malfatti 2006), which may increase the toxicity of the amphetamines that are bioactivated by this pathway. Some flavonoids (quercetin, luteoline, apigenine, baicalein, crissine, flavones) can induce simultaneously phase I (CYP450) and phase II (UGTs) enzymes. Other naturally occurring compounds that can also induce the UGTs are cumarine, elagic acid, and ferulic acid (Felton and Malfatti 2006).

Finally, there are several nutritional factors that can affect the expression of CYP and therefore the amphetamines toxicity such as: changes in the consumption of macronutrients (e.g., proteins, carbohydrates, lipids), changes in the levels of micronutrients (e.g., vitamins, metallic ions), fasting and reduction of the caloric intake, and the “non-nutrients” present in the diet (e.g., dioxins, antibiotics, growth-promoting hormones, environmental pollutants, pesticides, mycotoxins, products delivered from the packaging material, products generated during food processing, food additives, etc.) (Ioannides 1999).

From all the information compiled in this section, it is clear that the effects caused by the ingestion of an amphetamines pill can be affected by many different factors, which hampers the attribution of the observed effects only to the amphetamines. Particularly worrying are the interactions that may arise between amphetamines and other drugs co-consumed intentionally or inadvertently and that can be fatal.

Therefore, it is crucial to understand the influence of all these factors on amphetamines toxicity to establish risk prevention measures and develop novel and more effective preventive strategies to decrease risks of amphetamines consumers.

Acknowledgements The authors are grateful to Fundação para a Ciéncia e Tecnologia (FCT) for grant Pest/C/EQB/LA0006/2011 and to the project [PTDC/SAU-FCF/102958/2008]–QREN initiative with EU/FEDER financing through COMPETE. VMC and JPC acknowledge FCT for their Post-doc grants (SFRH/BPD/63746/2009 and SFRH/BPD/30776/2006).

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