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Review

The neurotoxicity of amphetamines during the adolescent period

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ABSTRACT

Amphetamine-type psychostimulants (ATS), such as amphetamine (AMPH), 3,4-methylenedioxymethamphetamine (MDMA), and methamphetamine (METH) are psychoactive substances widely abused, due to their powerful central nervous system (CNS) stimulation ability. Young people particularly use ATS as recreational drugs. Moreover, AMPH is used clinically, particularly for attention deficit hyperactivity disorder, and has the ability to cause structural and functional brain alterations. ATS are known to interact with monoamine transporter sites and easily diffuse across cellular membranes, attaining high levels in several tissues, particularly the brain. Strong evidence suggests that ATS induce neurotoxic effects, raising concerns about the consequences of drug abuse.

Considering that many teenagers and young adults commonly use ATS, our main aim was to review the neurotoxic effects of amphetamines, namely AMPH, MDMA, and METH, in the adolescence period of experimental animals. Reports agree that adolescent animals are less susceptible than adult animals to the neurotoxic effects of amphetamines. The susceptibility to the neurotoxic effects of ATS seems roughly located in the early adolescent period of animals. Many authors report that the age of exposure to ATS is crucial for the neurotoxic outcome, showing that the stage of brain maturity has a strong importance. Moreover, recent studies have been undertaken in young adults and/or consumers during adolescence that clearly indicate brain or behavioural damage, arguing for long-term neurotoxic effects in humans. There is an urgent need for more studies during the adolescence period, in order to unveil the mechanisms and the brain dysfunctions promoted by ATS.

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Abbreviations: [^{123}I]-β-CIT, ^{123}I-labelled 2b-carbomethoxy-3b-(4-iodophenyl) tropane; 5-HIAA, 5-hydroxyindoleacetic acid; 5-HT, 5-hydroxytryptamine, serotonin; 5-HTT, serotonin transporter; ADHD, attention deficit hyperactivity disorder; AMPH, amphetamine; ATS, amphetamine-type psychostimulants; CNS, central nervous system; DA, dopamine; DAT, dopamine transporter; DOI, 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane; DOPAC, dihydroxiphenylacetic acid; fMRI, functional magnetic resonance imaging; GFAP, glial fibrillary acidic protein; h, hour; HVA, homovanillic acid; i.m., intramuscular; i.p., intraperitoneal; MAO, monoamine oxidase; MDMA, 3,4-methylenedioxymethamphetamine; METH, methamphetamine; NE, norepinephrine; NET, norepinephrine transporter; PND, postnatal day; p.o., *per os*; s.c., subcutaneous; SPECT, single photon emission computed tomography; TH, tyrosine hydroxylase; TPH, tryptophan hydroxylase; TUNEL, terminal deoxynucleotidyl transferase-mediated biotin-dUTP nick-end labelling; UNODC, United Nations Office of Drugs and Crime; VMAT, vesicular monoamine transporter.

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1. Introduction

Amphetamines are psychoactive substances and members of the phenylethylamine family, which include a broad range of substances that may be stimulant, euphoric, anorectic, entactogenic, or hallucinogenic agents (Carvalho et al., 2012). Amphetamine (AMPH) has a phenyl ring, a two carbon side chain between the phenyl ring and the nitrogen, an α-methyl group, and a primary amino group (Fig. 1). This basic structural feature is shared by other amphetamine-type psychostimulants (ATS) that enable their characteristic pharmacological actions (Sulzer et al., 2005). AMPH, methamphetamine (METH), and 3,4-methylenedioxymethamphetamine (MDMA or "ecstasy") are widely abused amphetamine-like synthetic drugs, with the basic chemical structure of phenylethylamine. AMPH, METH, and MDMA may be ingested, snorted, and less frequently, injected, and they can be taken in form of tablet, powder, or capsule, and, regarding METH, the crystalline form can also be smoked (EMCDDA, 2014). The typical recreational use of AMPH, MDMA, or METH is often characterized by a pattern of repeated frequent administrations during a short time period, also known as a binge administration (Badon et al., 2002).

According to the World Drug Report 2014 of the United Nations Office of Drugs and Crime (UNODC), ATS are the second most commonly used illicit substances. The illicit drug abuse is commonly related with nightlife, which is more frequently attended by young people, but it can also be associated with some specific social contexts and cultural groups (EMCDDA, 2014; UNODC, 2014). Among ATS, AMPH, and MDMA are the most available in Europe, meanwhile METH abuse is a great cause of concern in North America (EMCDDA, 2014; UNODC, 2014).

Considering that ATS are commonly used by many teenagers and young adults, we aimed to review the neurotoxic effects of amphetamines, namely AMPH, MDMA, and METH, to the young brain of experimental animals. Additionally, we reviewed some recent works regarding the consumption in young adolescent and its neurotoxic consequences. Out of the scope of this review are the acute toxic effects of amphetamines to the peripheral organs and death related events, which have been reviewed elsewhere in detail (Carvalho et al., 2012).

2. Pharmacology

ATS are psychostimulants known to interact with monoamine transporter sites in the central nervous system (CNS). Amphetamines act as substrates for the membrane transporters of norepinephrine (NET), dopamine (DAT), and serotonin (5-HTT), due to the structural similarity with monoamine neurotrans-

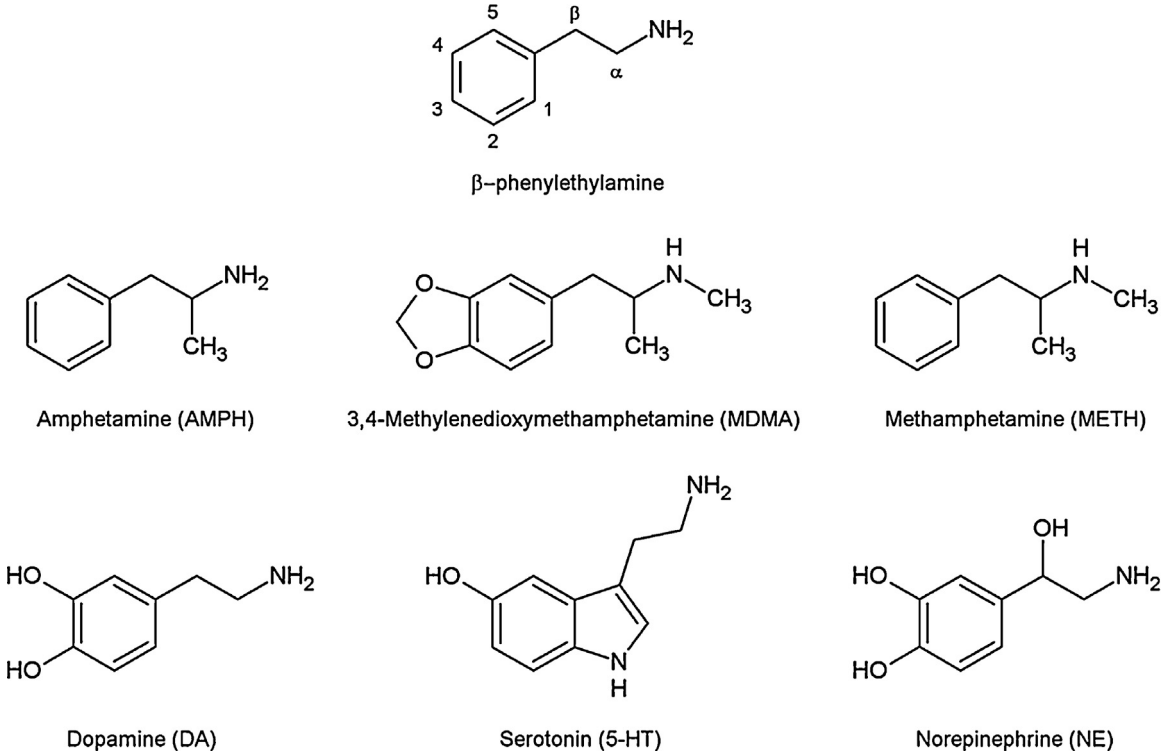

Fig. 1. Chemical structures of β-phenylethylamine (numbered), amphetamine (AMPH), 3,4-methylenedioxymethamphetamine (MDMA or "Ecstasy"), and methamphetamine (Meth, "Ice"). Amphetamines are structurally related to the monoamine neurotransmitters dopamine (DA), serotonin (5-HT), and norepinephrine (NE).

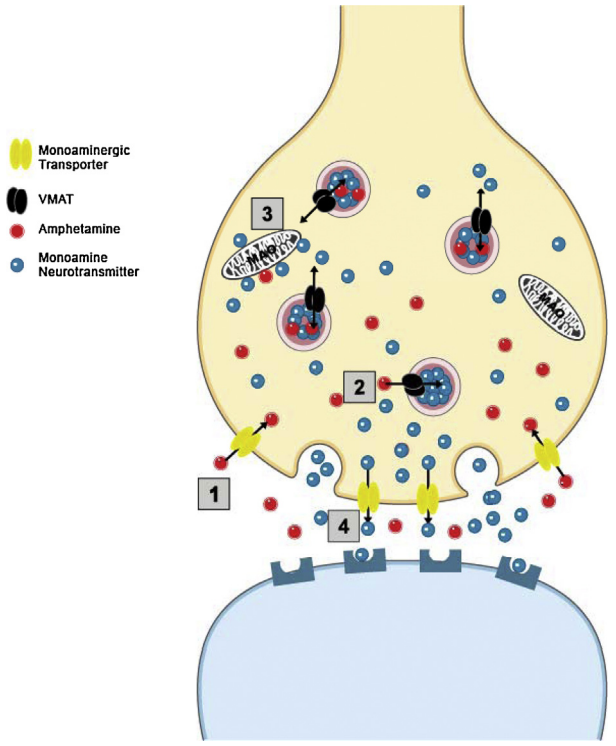

Fig. 2. General pharmacological mechanism of action of amphetamines at the monoaminergic neuron. Amphetamines are substrates of monoamine transporters, and enter the neuron through that route (1). Amphetamines differ in their affinity to the different monoamine transporters. Once inside the neuron they access the neurotransmitter vesicles, *via* the vesicular monoamine transporter (VMAT), and promote the disruption of vesicular storage increasing the free cytosol neurotransmitter content (2). The free neurotransmitter content is also increased by the inhibition of monoamine oxidase (MAO) metabolism promoted by amphetamines (3). Given the massive increase of neurotransmitter in the cytosol the monoamine transporter activity is reversed, and promotes the nonvesicular release of neurotransmitters (4). The huge increase in the neurotransmitter at the synaptic cleft enhances the monoaminergic transmission.

mitters, norepinephrine (NE), dopamine (DA), and serotonin (5-hydroxytryptamine; 5-HT) (Fig. 1) (Berger et al., 1992; Crespi et al., 1997; Jones et al., 1998; Kegeles et al., 1999; Rothman et al., 2000; Silvia et al., 1996). Thereby, ATS reduce the uptake of endogenous neurotransmitters to the cytoplasm and favour the reverse transport of endogenous neurotransmitters into the synaptic cleft, resulting in non-exocytotic neurotransmitter release (Fig. 2) (Berger et al., 1992; Crespi et al., 1997; Sulzer et al., 1995). Amphetamines can also elevate cytoplasmic transmitter concentrations by promoting DA and 5-HT release from storage vesicles *via* vesicular monoamine transporter (VMAT), while preventing the uptake into vesicles, making neurotransmitters more readily available for reverse transport (Jones et al., 1998; Partilla et al., 2006; Rothman and Baumann, 2003; Sulzer et al., 1995).

Although AMPH and its analogues present similar actions at several transporters, its principal mechanism of action is increasing release of monoamines from the presynaptic nerve terminals (Jones et al., 1998; Kegeles et al., 1999; Silvia et al., 1996). Thus, AMPH enters the cell by acting on DA terminals. This entrance can occur *via* DAT, which is the most common route, or, it also can happen by AMPH lipophilic diffusion through the plasma membrane, which is more efficient at higher AMPH concentrations. The presence of the α-methyl group leads to an increased ability to cross membranes due to its amphipathic nature. Moreover, the chemical structure of AMPH prevents monoamine oxidase (MAO) enzyme ability to oxidise the primary amine due to the presence of the α-methyl group (Fig. 1) (Carvalho et al., 2012; Jones et al., 1998). In general, DA is mostly increased by AMPH in the synaptic cleft, by the mechanisms of reverse transport of VMAT and DAT, as referred above (Jones et al., 1998; Partilla et al., 2006; Sulzer et al., 1995).

In normal conditions, DA is metabolised to dihydroxiphenylacetic acid (DOPAC) by MAO (Davidson et al., 2001). AMPH also influences DA-metabolic pathways, decreasing the levels of DOPAC, as a result of AMPH-induced MAO inhibition, thus prolonging the monoaminergic transmission (Jones et al., 1998; Miller et al., 1980; Taylor et al., 2013).

Likewise, METH is also an indirect monoaminergic agonist. It is a substrate of NET, DAT, and 5-HTT and increases the levels of NA, DA, and 5-HT in the synaptic cleft, by acting on their reuptake and also on the storage vesicles (Brown et al., 2000; Cruickshank and Dyer, 2009; Rothman et al., 2000). METH also prolongs monoaminergic transmission by inhibiting MAO activity, which results in an additional increase of cytosolic DA (Larsen et al., 2002).

MDMA interaction with the monoaminergic system is similar to that of AMPH and METH, but it has more significant effects on the 5-HT system, namely, inducing the reverse transport of 5-HT *via* 5-HTT and VMAT (Baumann et al., 2005; Berger et al., 1992; Crespi et al., 1997; Green et al., 2003; Partilla et al., 2006; Wichems et al., 1995). The cytoplasmatic non-vesicular stored 5-HT should, in normal conditions, be degraded by MAO, however as MDMA is a competitive inhibitor of MAO-A activity, it will contribute to the accumulation of extracellular 5-HT after MDMA exposure (Leonardi and Azmitia, 1994).

In summary, amphetamines differ in their affinities for monoamine transporters, therefore resulting in the disruption of pathways related to different neurotransmitters. AMPH and METH have more potent actions on DA release rather than 5-HT release, while MDMA shows greater affinity for 5-HTT over DAT. Accordingly, MDMA causes a higher release of 5-HT instead of DA. Importantly, AMPH, METH, and MDMA are more potent NE releasers, rather than DA and 5-HT releasers (Rothman and Baumann, 2003).

Table 1 summarizes some of the major findings regarding the pharmacodynamics of AMPH, MDMA, and METH.

3. The evidence of neurotoxicity in adult laboratory animals

For the purpose of this review, we have considered neurotoxicity after amphetamines exposure as: (1) neuroanatomical changes to the CNS, and (2) functional neurotoxic changes to the CNS including neurochemical deficits, neurophysiological or behavioural effects (cognitive dysfunction, for instance). The neurotoxic effects of amphetamines have been vastly studied and their ability to damage brain monoaminergic cells was proven, namely by causing long-term deficits in dopaminergic and serotoninergic systems in several brain areas of animals (Commins et al., 1987; Gibb et al., 1997; Ricaurte et al., 1982; Schmidt, 1987; Sonsalla et al., 1996; Villemagne et al., 1998). Importantly, the neurotoxic actions of amphetamines have been evaluated by biochemical (decreased levels of monoamines and their major metabolites, decreased monoamine transporter binding sites, and lower expression and/or activity of enzymes involved in the synthesis or metabolism of neurotransmitters), histological, and immunocytochemical techniques. Additionally, amphetamines are known to promote neurobehavioral deficits, such as cognitive impairments and memory deficits, as well as anxiety or depression symptoms. In the present section, we briefly review the literature regarding the neurotoxic actions of amphetamines conducted in adult laboratory animals, which constitute the vast majority of published reports.

One of the major neurotoxic actions of amphetamines observed in laboratory animals is the sustained depletion of monoamine

Table 1
Findings related with amphetamines' pharmacological mechanisms of action.

Findings	References
In vivo studies in rats demonstrate that AMPH acts as a DA releaser.	(Chiueh and Moore, 1975; Sulzer and Rayport, 1990; Von Voigtlander and Moore, 1973)
Studies in the mouse brain indicated that MDMA causes an efflux of 5-HT, DA, and NA.	(Johnson et al., 1986; Nichols et al., 1982)
It was shown that MDMA interacts with monoamine carriers, leading to a non-exocytic release of 5-HT, DA, and NA, in the mouse brain.	(Berger et al., 1992; Crespi et al., 1997)
In vivo microdialysis showed that MDMA induces DA and 5-HT release in the rat brain, and the effects of the drug on 5-HT release were predominant.	(Baumann et al., 2005; Yamamoto and Spanos, 1988)
Experiments *in vitro* using *Planorbis corneus* giant dopamine cells indicated that AMPH decreases vesicular DA content, and redistributes the neurotransmitter to the cytosol, promoting reverse transport, and DA release.	(Sulzer et al., 1995)
Experiments in human embryonic kidney 293 cells indicated that AMPH is a substrate of the human DAT.	(Sitte et al., 1998)
Studies with DAT knockout (DAT −/−) mice, after AMPH administration, have shown that despite increased cytosolic DA concentrations through vesicular depletion, the synaptic levels of DA remained unchanged, since no DAT is available for transporter-mediated release.	(Jones et al., 1998)
In vitro studies in rats demonstrated that the 5-HTT uptake blocker fluoxetine inhibited the calcium-independent release of 5-HT after MDMA/METH, demonstrating that MDMA and METH induce release of cytoplasmic 5-HT *via* 5-HTT.	(Berger et al., 1992; Wichems et al., 1995)
Studies in rats demonstrated that the ability of AMPH and METH to release DA is directly proportional to the dose.	(Kuczenski et al., 1995)
In rats, METH causes dose-dependent release of DA, NE, and 5–HT, and is more potent in the release than in the reuptake inhibition assay.	(Rothman et al., 2000)

brain levels. A study in rats clearly proved this neurotoxic action, since repeated injections of d-AMPH [17 mg/kg, subcutaneous (s.c.), twice daily] to rats resulted in the decrease of brain NE levels. These effects persisted for several days after the last injection of the drug (McLean and McCartney, 1961).

MDMA also exhibits the ability of depleting monoamine neurotransmitter content in the rats' brain. Several studies reported depletion in brain 5-HT levels after MDMA administration (Aguirre et al., 1998a; Colado et al., 1993; Colado et al., 1995; Commins et al., 1987; O'Shea et al., 1998; Schmidt, 1987; Shankaran and Gudelsky, 1999). In fact, Schmidt demonstrated that the 5-HT depletion caused by 10 mg/kg, s.c. administration, of MDMA has a biphasic response. The first phase shows a reversible depletion of 5-HT, in which 5-HT concentrations declined to 16% of control, 3 hours (h) after administration. Following this initial decline, a recovery of 5-HT levels occurred, thus returning to basal levels, between 6 and 24 h. The second phase is characterized by a long-term 5-HT depletion in the days following MDMA administration: after a week the 5-HT levels declined to 74% of control (Schmidt, 1987).

METH also causes severe depletion in brain monoamine levels. Repeated s.c. administration of high doses of METH (50 and 100 mg/kg/daily, for four days) to rats resulted in a dose-related decrease in DA levels and its uptake sites in the striatum, two weeks after the last administration. No changes in brain NE levels were reported after this regimen of repeated METH administration when compared to controls (Wagner et al., 1980). Of note, the researchers stated in the methods section of that report that the highest daily dose of 100 mg/kg promoted about 50% of lethality to rats (Wagner et al., 1980).

Studies regarding the ability of AMPH, MDMA, and METH to deplete monoamine neurotransmitter content, after administration to laboratory animals, are summarized in Tables 2, 3, and 4, respectively.

The neurotoxic action of amphetamines also involves the degeneration of neuronal fibres. MDMA was shown, in several studies, to be able to promote damage to the nerve terminals (Commins et al., 1987; O'Hearn et al., 1988; O'Shea et al., 1998; Schmidt, 1987). By using an immunocytochemical technique, O'Hearn et al. were able to demonstrate the structural damage to the terminal

Table 2
Studies related to the neurotoxicity of AMPH in adult laboratory animals.

Dosage Regimen	Studies	Reference
10 mg/kg, s.c., twice daily, 2 h interdose interval	A study in rabbits demonstrated a reduction in NE levels in the superior cervical ganglia and in the brain 4 h after the first administration of d-AMPH.	(Sanan and Vogt, 1962)
9.2 mg/kg, i.p., single dose	A single injection of d-AMPH administered to rats pre-treated with iprindole (interferes with the metabolism of AMPH and prolongs its half-life) resulted in the destruction of DA nerve terminals two weeks after the treatment.	(Ricaurte et al., 1984)
0.1 or 0.25 mg/kg, s.c., twice daily, for 5 days	Prolonged exposure of rats to AMPH at doses near threshold for locomotor activation, and within the therapeutic range for attention deficit hyperactivity disorder (ADHD) treatment, can produce sensitization-like effects on the locomotor response to a subsequent exposure. Four days after the last treatment, animals received another 0.5 mg/kg of AMPH, which promoted a marked increase in locomotor response.	(Kuczenski and Segal, 2001)
0.1–1.0 mg/kg, intramuscular (i.m.), twice daily, for 6 or 12 weeks	A research in rhesus monkeys reported that the AMPH-sensitized monkeys were deeply impaired in their ability to acquire cognitive tasks, since several months after the treatment with AMPH, the monkeys had profound and enduring deficits in the acquisition of a spatial working memory task, and spatial delayed response.	(Castner et al., 2005)

Table 3
Studies related to the neurotoxicity of MDMA in adult laboratory animals.

Dosage Regimen	Studies	Reference
10, 15, or 20 mg/kg, i.p., single dose	A single dose of MDMA resulted in significant loss of 5-HT and decreases in the 5-HT major metabolite, 5-hydroxyindoleacetic acid (5-HIAA) in rats' brain, seven days after the administration of 10 or 15 mg/kg, or four days after 20 mg/kg.	(Colado et al., 1993; Colado et al., 1995; O'Shea et al., 1998).
4 × 10 mg/kg, i.p., every 2 h	A study in rats reported a 45% depletion of 5-HT levels one week after several doses of MDMA.	(Shankaran and Gudelsky, 1999)
10, 20, or 40 mg/kg, s.c., twice daily, for 4 days; or 40 mg/kg, s.c., single dose	In rats Commins et al. reported depletions of 5-HT after repeated injections of MDMA and, also, after a single administration of a higher dose of the drug, two weeks after exposure to MDMA. It was also observed nerve terminal degeneration in the striatum.	(Commins et al., 1987)
5 mg/kg, s.c., twice daily for 4 days	In a study performed in squirrel monkeys, was observed the reduction of brain serotonergic innervations and 5-HT levels following MDMA exposure. The serotonergic innervations still remained reduced seven years after exposure to the drug, showing that the damage to serotonergic system is, probably, irreversible.	(Hatzidimitriou et al., 1999)
10, 15, 20 mg/kg, i.p., twice daily, for 3 days	After a neurotoxic exposure of rats to MDMA, it was reported a long lasting cognitive impairment over the 16 days following the exposure.	(Marston et al., 1999)

portions of axons, promoted by MDMA, in rats. Two weeks after the administration of MDMA (20 mg/kg, s.c., twice a day for four days) fragmented 5-HT axons were observed in the forebrain. These fragmented axons are an anatomic evidence for the degeneration of 5-HT projections (O'Hearn et al., 1988). METH was also shown to induce terminal degeneration in laboratory animals. Ricaurte et al. reported that METH (3 × 50 mg/kg, s.c., every 8 h) induced destruction of DA terminals, along with related DA neurochemical deficits in the striatum and nucleus accumbens of rats, even three weeks after the administration (Ricaurte et al., 1982). Several studies related with the degeneration of neuronal fibres induced by AMPH, MDMA and METH are summarized in Tables 2, 3, and 4, respectively.

In addition to the damage to dopaminergic and serotoninergic neuronal systems, amphetamines can also induce neuronal death. Using a terminal deoxynucleotidyl transferase-mediated biotin-dUTP nick-end labelling (TUNEL) histochemical method to verify DNA fragmentation, Krasnova et al. reported that the intraperitoneal (i.p.) administration of AMPH (10 mg/kg, four times, every 2 h) to mice resulted in the death of non-dopaminergic cells in the striatum, the maximal cell death occurring four days after AMPH injections (Krasnova et al., 2005). In several studies, MDMA administration to mice and rats produced neuronal death in several brain areas including the cortex, hippocampus, amygdala, ventromedial/ventrolateral thalamus, and tenia tecta (Armstrong and Noguchi, 2004; Commins et al., 1987; Meyer et al., 2004; Schmued, 2003; Tamburini et al., 2006; Warren et al., 2007). METH-induced neuronal death was also investigated in the brain of mice and rats, and it was observed in several areas, namely the striatum, cortex, hippocampus, indusium griseum, and medial habenular nucleus (Armstrong and Noguchi, 2004; Deng et al., 2001; Warren et al., 2007; Zhu et al., 2006). Corroborating these *in vivo* findings, several *in vitro* studies demonstrated that AMPH, METH, and MDMA induced neuronal apoptosis in cultured neurons of the rat cor-

Table 4
Studies related to the neurotoxicity of METH in adult laboratory animals.

Dosage Regimen	Studies	Reference
4 × 10 mg/kg, i.p., every 2 h	Rats treated with a neurotoxic regimen of METH, presented a reduction of DA contents in caudate nucleus (56%) and nucleus accumbens (30%) one week later. The levels of 5-HT were also decreased in caudate nucleus (50%) and nucleus accumbens (63%).	(Wallace et al., 1999)
4 x 10 mg/kg or 4 x 20 mg/kg,i.p., every 2 h	A study in mice demonstrated a marked depletion of striatal DA (≥90%) seven to eight days after METH administration.	(Sonsalla et al., 1996)
4 × 15 mg/kg, s.c., 2 h apart	A study in mice observed neuronal degeneration in the indusium griseum, tenia tecta, and fasciola cinerea, five days after METH exposure.	(Schmued and Bowyer, 1997)
4 × 4 mg/kg, s.c., 2 h apart	Repeated administration of METH doses to rats induced long-term damage to striatal DA and forebrain 5-HT terminals, and somatosensory cortical neurons degeneration. The exposed animals also presented impairments in memory one and three weeks after the exposure.	(Marshall et al., 2007)
3 × 10 mg/kg, i.p., 2 h apart	A study in rats observed depletion of DA and 5-HT content in striatum and impairments in behavioural tasks after exposure to METH.	(Bisagno et al., 2002)
1.25 mg/kg, p.o., given twice, 4 h apart	A study in squirrel monkeys treated with METH reported decreases in striatal dopaminergic markers one week after treatment. Moreover, the study was conducted in two different ambient temperatures (26 and 33 °C), and the ones treated at the highest ambient temperature had the largest dopaminergic deficits.	(Yuan et al., 2006)
0.2 mg/kg or 2 × 2 mg/kg, i.m., 24 h apart	Studies with vervet monkeys demonstrated that after a long-term exposure to METH there is a decrease in phenotypic markers of the DA system. Decreases in striatal DA content were reported, as well as decreases in DAT, tyrosine hydroxylase (TH), and VMAT.	(Harvey et al., 2000; Melega et al., 2007)

tex and in cerebellar granule neurons (Capela et al., 2007, 2006a, 2006b; Jiménez et al., 2004; Stumm et al., 1999).

The neurotoxic actions of amphetamines were also reported in non-human primates. One example of a study was conducted by Scheffel et al. in which 5 mg/kg MDMA was injected to baboons, s.c., twice a day, for four days, and animals were sacrificed 13, 19, and 40 days, or 9 and 13 months after the last dose of the drug. In experiments conducted for short periods after the treatment with MDMA (13–40 days) a substantial loss of 5-HTT was observed in all areas of the brain examined. Meanwhile, 9 and 13 months after administration, this loss was only reported in neocortical areas. In fact, no reductions of 5-HTT were observed in the hypothalamus and midbrain, between 9 and 13 months after MDMA, and there was a recovery and an increase in the binding sites when compared to controls (Scheffel et al., 1998). Other studies related with the neurotoxic actions of AMPH, MDMA, and METH in non-human primates are summarized in Tables 2, 3, and 4, respectively.

The use of ATS can have other consequences, namely in animals' behaviour. Segal and Kuczenski observed that a repeated exposure to AMPH [2.5 or 4.0 mg/kg, s.c., multiple sessions (four injections a day at 2 h intervals)] resulted in an increase in the magnitude of post-stereotypy locomotor activation with a continuous state of extreme agitation, seen by the locomotor response pattern to the 4th injection of the 15th session. Additionally, after a challenge with 2.5 mg/kg of AMPH, three days after the last injection of the 15th session, a persistent AMPH-induced behavioural pattern (like nose-poking) occurred, and the post-stereotypy locomotion remained elevated (Segal and Kuczenski, 1997).

MDMA can also affect the animals' behaviour. Spanos and Yamamoto reported that after repeated injections of MDMA (2.5, 5.0, and 7.5 mg/kg, i.p.) to rats, the stereotypic locomotor behaviour and the serotonin syndrome were augmented, which suggest that, like AMPH, MDMA can produce behavioural sensitization (Spanos and Yamamoto, 1989). A long-term effect of MDMA exposure (three to four weeks after the administration) is the decrease in social interaction, contrarily to MDMA acute effects that induce increase sociability (Bull et al., 2003; Clemens et al., 2004; Fone et al., 2002). Other studies in rats also report that MDMA induces long-term and persistent anxiety-like behaviours (Baumann et al., 2007; Bull et al., 2004; Clemens et al., 2004).

METH is also known to interfere with animal behaviour and the experimental animals' cognitive function. Segal and Kuczenski observed that a repeated exposure to METH (2.76 or 4.42 mg/kg, s.c., four daily injections, 2 h apart) led to an increase in the magnitude of post-stereotypy locomotor activation, and that the METH response is markedly longer than the AMPH response in male Sprague-Dawley rats (Segal and Kuczenski, 1997). Besides, a neurotoxic regimen of METH can also induce impairment of working memory, both spatial and non-spatial working memory in rats (Nagai et al., 2007; Schröder et al., 2003). Decreased social interaction and increased anxiety were reported after METH exposure in either Wistar rats or Vervet monkeys (Clemens et al., 2004; Melega et al., 2007). In Tables 2, 3, and 4 are presented studies related with changes in animals' behaviour and cognitive function induced by AMPH, MDMA, and METH, respectively.

4. The neurotoxicity of amphetamines to adolescent laboratory animal models

Amphetamines are commonly used as illicit recreational drugs by many teenagers and young adults. Several studies showed that it can greatly affect their cognitive skills, which may be reflected during their lifetime (King et al., 2010; Kish et al., 2010; McCann et al., 1999). The prevalence of amphetamines usage is higher in adolescents and young adults (EMCDDA, 2014), and therefore there is an increased need to perform more studies regarding the consequences of exposure to these drugs during the adolescent period (Spear, 2000). For that reason, researchers mimic the exposure of human adolescents by conducting experiments with laboratory animals corresponding to that developmental period. It is not simple to make age comparisons between humans and the laboratory animal models mice or rats, although, in the literature, the age ranges of the development stages of these laboratory animals are mostly divided in: (1) the neonatal period, considered from postnatal day (PND) 1 to 27; (2) the early adolescence period, considered from PND 28 to 37; (3) the middle adolescence period, considered from PND 38 to 51; (4) the late adolescence period, considered from PND 52 to 60; and (5) the young adulthood, that starts at PND 60 (Cox et al., 2014; Morley-Fletcher et al., 2002; Quinn, 2005). Importantly, there are not many studies that compare the effects of equivalent treatment regimens under identical conditions in animals at different developmental stages, and those studies are most relevant.

Adolescence is characterized by neurobiological processes that influence behaviour and general skills during adulthood. The use of amphetamines sometimes starts in this developmental period and the early use of these drugs has been found to predict the development of drug addiction and mood disorders in adulthood (Chambers et al., 2003; Chen et al., 2009; Laviola et al., 1999; Spear, 2000). The neurological alterations after ATS misuse in adolescence have been proven in animal studies, as it will be detailed below. For a more visual insight, we have elaborated figures to summarize the neurotoxic dose regimens of ATS in the adolescent period of the rat model (Figs. 3–5).

Another important issue when analysing studies in animals are the relevance to the human situation of the administrated doses. To estimate the equivalence of the dose regimens to the human situation, the allometric scaling principles can be used using the formula "$dose\ human\ (mg/kg) = dose\ animal\ (mg/kg) \times (animal\ weight/human\ weight)^{1/4}$" (Hayes and Kruger, 2014). According to those principles of allometric scalling a dose of 5 mg/kg of AMPH in an adolescent rat is approximately equivalent to 59 mg in a 50 kg adolescent human. AMPH daily doses of 30 mg are used therapeutically to treat attention deficit hyperactivity disorder "(ADHD)" (Kish, 2008). As for METH, a dose of 10 mg/kg in an adolescent rat is approximately equivalent to 117 mg in a 50 kg adolescent human. A single dose (the amount in a smoking pipe) of crystal METH sufficient to cause a "significant rush" has been reported to be about 40–60 mg, and many users take repeated doses of the drug in a binge pattern (Kish, 2008). As for MDMA, a dose of 15 mg/kg in an adolescent rat, which is generally accepted neurotoxic dose to adult animals, is approximately equivalent to 180 mg in a 50 kg adolescent human. Since, human abusers usually take about 80–250 mg per session, most of them using the binge dosing pattern (Capela et al., 2009), thus a dose of 15 mg/kg would represent an intake of two to three pills per night.

4.1. Amphetamine

AMPH is commonly used in humans in the therapy for ADHD, a disease that specially affects children and adolescents (Kutcher et al., 2004). Despite many years of therapeutic experience with this drug, concerns are still raised regarding the possible neurotoxic effects that could occur when it is chronically used. Soto et al. performed a study in peri-adolescent rhesus monkeys and the cognitive, behavioural, physiological and *in vivo* neurochemical parameters were assessed. For 18 months, the juvenile male monkeys (24 months of age) received a methylphenidate solution (12–16 mg/kg) or a dl-AMPH mixture (0.7–0.8 mg/kg), with doses comparable to the therapeutic levels used in children, twice daily, seven days a week. Researchers found no differences to con-

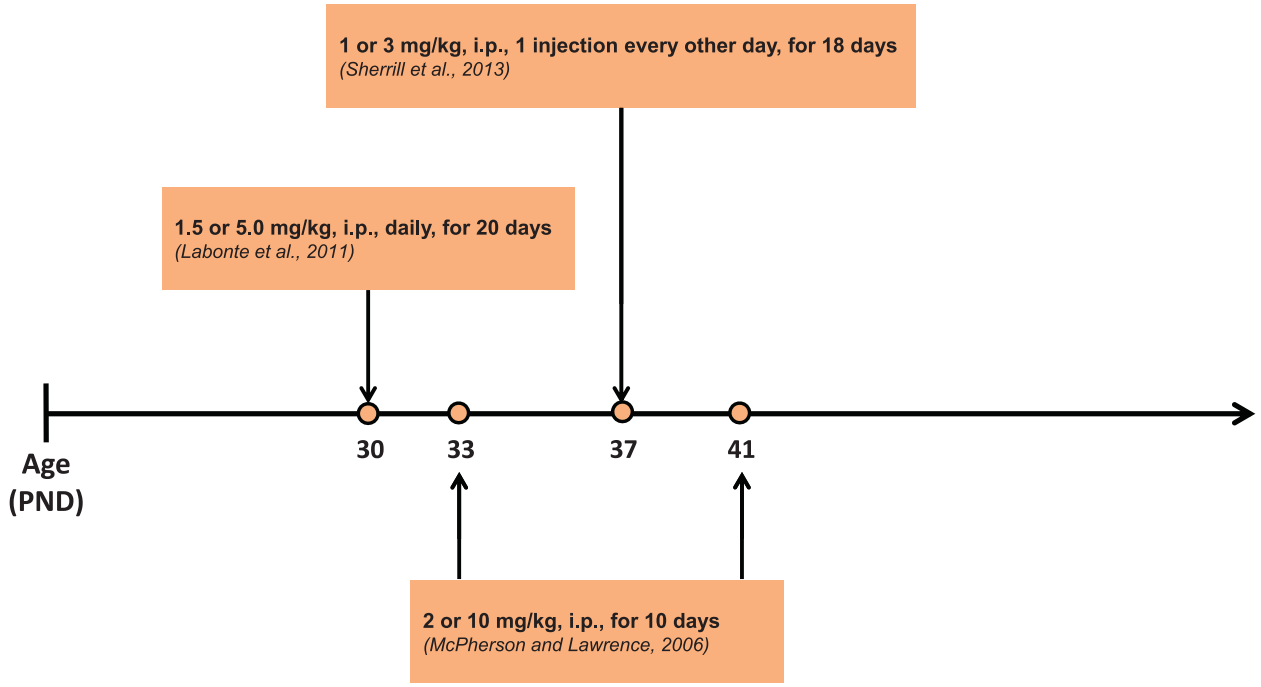

Fig. 3. Schematic representation of the different AMPH dose regimens that promoted neurotoxic changes in behaviour and cognitive functions when AMPH was administered at different developmental stages of rats. Orange squares ( ) represent the adolescent period (PND – postnatal days). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

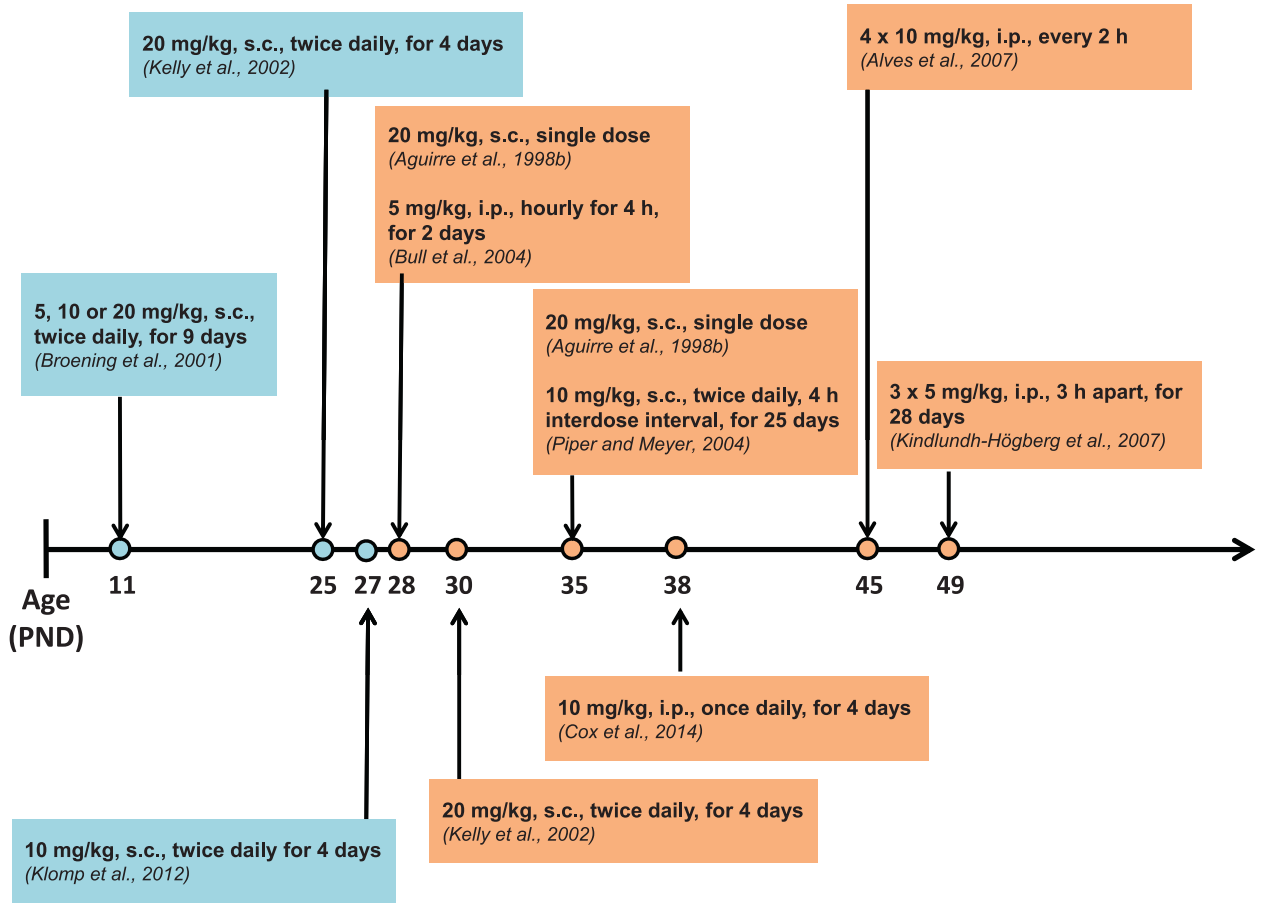

Fig. 4. Schematic representation of the different MDMA dose regimens that promoted neurotoxic changes to the serotonergic system, as well as changes in behaviour and on cognitive functions when administered at different developmental stages of rats. Blue squares ( ) represent the neonatal period, and orange squares ( ) represent the adolescent period (PND – postnatal days). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

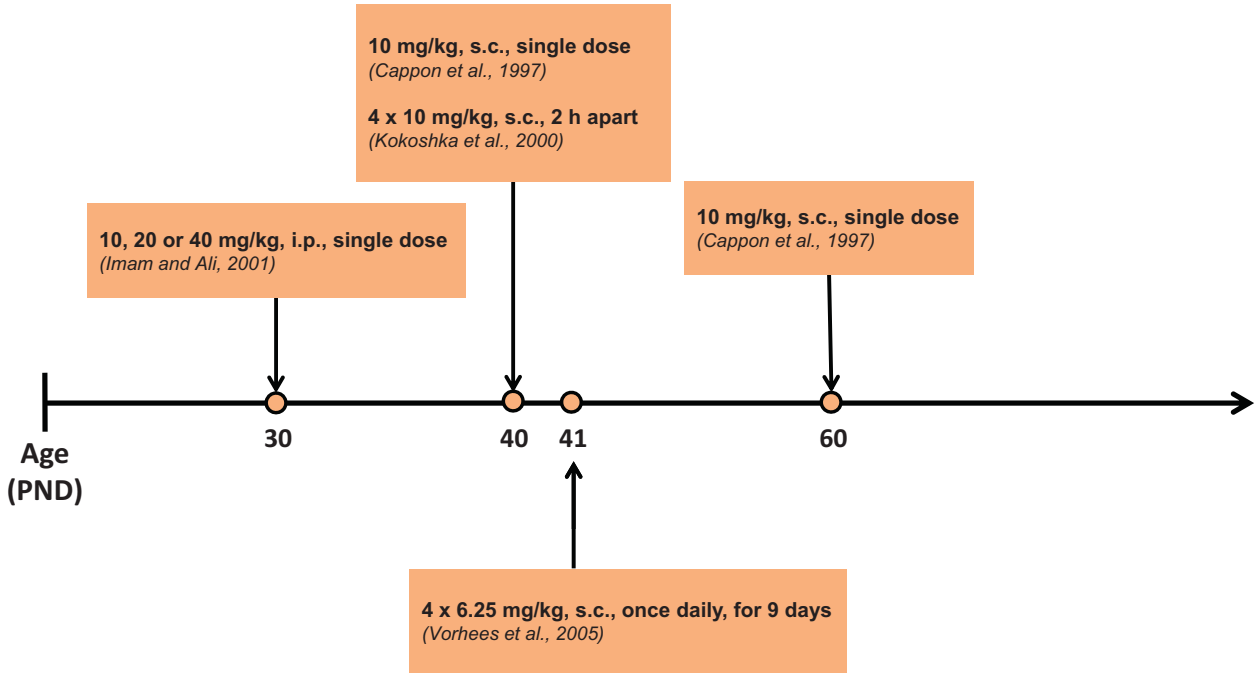

Fig. 5. Schematic representation of the different METH dose regimens that promoted deficits in the dopaminergic system, as well as impairment to cognitive functions when administered at different developmental stages of rats. Orange squares ( ) represent the adolescent period (PND – postnatal days). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

trol animals concluding that methylphenidate and AMPH have a reduced effect on cognitive, behavioural or physiological development on peri-adolescent non-human primates, when administered in a therapeutic range (Soto et al., 2012). Importantly, the animal model used in that study, the juvenile male monkeys, had no ADHD in contrast to the children and young adults that need this therapy. Despite not using animals with ADHD, this study used doses in the therapeutic human range arguing for the safety of AMPH in the clinical treatment of ADHD.

AMPH doses (0.5, 1.5, or 5.0 mg/kg, i.p.) were given daily to adolescent Sprague-Dawley rats from PND 30 to PND 50 and the behavioural profile and the firing activity of midbrain monoaminergic neurons were assessed later, namely during adulthood (between PND 71 and PND 85) under drug-free conditions (Labonte et al., 2011). The middle dose of AMPH (1.5 mg/kg) produced an increase in 5-HT and DA firing activity in adulthood, in contrast to the highest AMPH dose (5.0 mg/kg) that augmented NE firing, but not 5-HT or DA firing activity, when evaluated between PND 71 and PND 85. In addition, the adolescent AMPH exposure also induced an hyperlocomotion response between PND 71 and PND 85 in rats treated with 1.5 mg/kg dose, and all the three doses promoted higher risk of drug-taking behaviours during adulthood. These results suggest that AMPH exposure during adolescence may promote long-lasting neurophysiological alterations that influence their future behaviour (Labonte et al., 2011).

Adolescents are particularly susceptible to drug-induced neuroadaptations and cognitive changes, since their brain is still under development and undergoing anatomic and functional changes (Andersen et al., 2002; Smith, 2003). A recent study performed the administration of AMPH (1 or 3 mg/kg, i.p., one injection every other day) to adolescent rats from PND 37 to PND 55 and to adult rats from PND 98 to PND 116. This regimen induced long-lasting consequences on drug sensitivity and cognitive functions to adolescent rats (Sherrill et al., 2013). Adolescents were less sensitive to psychomotor effects of AMPH and more vulnerable to exposure-induced cognitive impairments, when compared to adult rats. The results demonstrated that the effects of AMPH on cognitive function depend on the age of exposure, and suggest that adolescent rats are more susceptible to amphetamine-induced neurobehavioral deficits (Sherrill et al., 2013).

A study on the performance of adolescent rats (PND 54) with a repeated intermittent administration of AMPH (1, 2 or 3 mg/kg, every other day) showed that the effects of repeated administration of the drug may interfere with cognitive processes, once a psychostimulant-sensitization led to attentional consequences (Deller and Sarter, 1998). There were increases in the number of false alarms, like "claims" for hits in non-signal trials, suggesting possible hyperattentional dysfunctions that may contribute to the development of psychotic symptoms (Deller and Sarter, 1998).

A study examined the reinforcing properties of AMPH (0, 1, 3.3, or 10 mg/kg, i.p.) in developing mice on PND 14–17, 21–24, or 28–31 (Cirulli and Laviola, 2000). The results indicated that AMPH-induced conditioned place preference was developed early. Moreover, this conditioned-place preference appeared earlier in females than in males. Also, AMPH increased, in a dose-dependent fashion, the locomotor activity and females were also more sensitive when compared to males. Females increased sensitivity to the locomotor activity effects of AMPH occurred between PND 14 and 21, with no significant changes at PND 21 and 28. The results suggest that AMPH-induced changes in adolescent mice, seem to depend on gender and age of exposure (Cirulli and Laviola, 2000).

McPherson and Lawrence performed a study in adolescent (PND 33–41) Sprague-Dawley rats, which were exposed to i.p. injections of 2 mg/kg or 10 mg/kg of AMPH, once daily, for ten days, followed by a four week period of abstinence and a subsequent rechallenge with AMPH (1.5 mg/kg, i.p.) (McPherson and Lawrence, 2006). The exposure to AMPH during the adolescence period promoted behavioural sensitization to an AMPH rechallenge in adulthood. The rechallenge with AMPH promoted a higher Fos expression in rats that were previously exposed to 10 mg/kg of AMPH when

comparing to those previously exposed to 2 mg/kg. Nevertheless, the sensitized locomotor activity was similar between the two groups. The researchers concluded that adolescent exposure to AMPH led to a neuronal sensitization in adulthood accompanied by a widespread neuronal activation as measured by an increase in Fos expression (McPherson and Lawrence, 2006).

In summary, it may be postulated that, in healthy animal models, AMPH impairs neurological functions. The exposure to AMPH during adolescence leads to long-lasting neurophysiological alterations, which reflects on the behaviour of animals. Adolescents are less sensitive to psychomotor effects of AMPH and more vulnerable to the cognitive impairments than adult animals. Moreover, the effects of AMPH on the cognitive function seem to be dependent on the age of exposure. Generally, studies do not compare the effects of equivalent treatment regimens under identical conditions in differential stages of maturity. However, a reason for using diverse dose regimens for different ages may rely on the dissimilar effects of AMPH according to the age of exposure. With that being said, it would be extremely useful to ascertain whether in a juvenile animal model of ADHD, the AMPH neurotoxicity would occur in the same fashion as observed in healthy adolescent animals. The neurotoxic doses of AMPH in the adolescent rat developmental stages are represented in Fig. 3.

4.2. "Ecstasy"

As mentioned previously in this review, MDMA induces neurotoxicity in adult animals, with alterations in the biochemical 5-HT markers, including depletion on the levels of 5-HT and its metabolite 5-hydroxyindoleacetic acid (5-HIAA), lower 5-HTT density and decreased activity of tryptophan hydroxylase (TPH) the 5-HT rate-limiting synthesis enzyme (Capela et al., 2009; Lyles and Cadet, 2003; Ricaurte et al., 2000).

Several studies indicate that perinatal or neonatal animals may be less sensitive to the neurotoxic effects of MDMA than adult animals (Aguirre et al., 1998b; Colado et al., 1997; Kelly et al., 2002; Klomp et al., 2012; Meyer and Ali, 2002; Meyer et al., 2004). Kelly et al. examined the toxicity induced by MDMA in the perinatal rat brain and its relation to the normal development of 5-HTT sites. They also determined whether early exposure to MDMA can alter brain function in future adult rats (Kelly et al., 2002). In this report, researchers evaluated perinatal development of 5-HTT sites by quantification of [^{3}H]-paroxetine binding autoradiography. Time-mated female Sprague-Dawley rats were injected s.c. with MDMA (20 mg/kg, twice daily) for four consecutive days, starting on gestational day 15 (E15), and neonatal male rats (from untreated dams) were also injected with MDMA (20 mg/kg, s.c., twice daily, for four consecutive days) on PND 10, 15, 20, 25, or 30. All animal groups mentioned were sacrificed on PND 40. Subsequently, another offspring group was injected with MDMA (20 mg/kg, s.c., twice daily, for four consecutive days) at PND 90 and, in this case, animals were sacrificed ten days after the drug treatment. The results showed no difference in the density of [^{3}H]-paroxetine binding sites, measured at PND 40, in brains of rats treated with MDMA from E15 to PND 20, when compared to controls. However, treatments with MDMA started on PND 25 or later resulted in significant reductions in [^{3}H]-paroxetine binding, with decreases of 46% at PND 25 and 63% at PND 30, when compared to controls. These decreased levels were not as significant as those found in rats treated with MDMA at PND 90, in which the density of [^{3}H]-paroxetine binding sites decreased by 90%. These results suggest that the susceptibility of serotonergic terminals to MDMA-induced neurotoxicity is absent in the immediate perinatal period; however, it is markedly increased when the treatment started on PND 25 and further, although not reaching the same extent as what is found in the adult rat brain (Kelly et al., 2002). In another paper, the lack of sensitivity of perinatal rats to the neurotoxic effects of MDMA was also reported. MDMA (20 mg/kg, s.c.) was given to pregnant female Wistar rats from E6 to E20, and the rat pups were sacrificed at PND 15 (Aguirre et al., 1998b). Other group of rats received a single dose of MDMA (20 mg/kg, s.c.) at PND 14, 21, 28, or 35, meanwhile adult (3-month-old) rats received the same regimen, and both groups were sacrificed seven days after MDMA treatment. The researchers observed that MDMA did not alter the density of [^{3}H]-paroxetine binding sites when MDMA was administered repeatedly during gestation or as a single dose at postnatal ages prior to PND 28. But when MDMA was administered at PND 35, 5-HTT density was significantly decreased in frontal cortex, seven days after the treatment. When exposure to MDMA occurred during the gestation period or at PND 14 and 21, it did not cause any significant reduction in 5-HT and 5-HIAA levels. However, at PND 28, MDMA induced a significant decrease in 5-HT and 5-HIAA in the hippocampus, seven days after the administration. Also, at PND 35, MDMA-induced long-term reduction of 5-HT and 5-HIAA levels in several brain areas. The reported data indicated that MDMA exposure during gestational periods or during early postnatal ages did not produce neurotoxicity to the serotonergic system. Authors concluded that the onset of susceptibility to this drug is placed between PND 28 and PND 35, in this animal model exposed to this MDMA regimen (Aguirre et al., 1998b).

Early post-natal exposure to MDMA may not promote neurotoxic damage, but that is not the case for adolescent/young animals. Several studies reported that exposure to MDMA during the adolescent period results in long-term reductions in 5-HT levels, as well as decreases in its major metabolite, 5-HIAA, and reduced 5-HTT binding sites (Bull et al., 2003, 2004; Morley-Fletcher et al., 2002; Piper et al., 2005; Piper and Meyer, 2004). A dose of MDMA (5 mg/kg, i.p.) was given hourly for 4 h on two consecutive days, to young Wistar rats at PND 28, and the involvement of the 5-HT_{2A} receptors in the long-term anxiogenic effect was evaluated (Bull et al., 2004). On PND 84, the rats pre-treated with MDMA showed a 27% decrease on social interaction, when compared to controls. Sixty days after the last MDMA injection, corresponding to PND 92, researchers observed significant reductions in hippocampal 5-HT and 5-HIAA concentrations, and 5-HT levels were also depleted in the frontal cortex and in the striatum. Moreover, the change in anxiety-related behaviour was also examined as a possible result of adaptations in the 5-HT_{2A} receptors function, by assessing the behavioural response evoked by the 5-HT_{2A} receptor agonist, 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI), to MDMA (5 mg/kg exposure to MDMA was followed by 1 mg/kg i.p. of DOI on PND 86). The results showed that the 5-HT and 5-HIAA depletions and the anxiogenic effect, after the repeated MDMA treatment, were accompanied by an attenuation of the anxiogenic response to DOI. Therefore, short-term exposure to MDMA might cause long-lasting reduction in specific 5-HT_{2A} receptor-mediated behaviour (Bull et al., 2004). Other studies, reported that serotonergic neurotoxicity was accompanied by an increased anxiety in the social interaction test in rats, 20–29 days after MDMA exposure (Bull et al., 2003; Fone et al., 2002). Other studies reported that intermittent MDMA administration throughout adolescence in rats can elicit tolerance to temperature deregulation and 5-HT syndrome evoked by the drug, and also produce later changes in performance of working memory and anxiety tests (Piper et al., 2005; Piper and Meyer, 2004). A study conducted by Piper and Meyer used adolescent rats that received MDMA (10 mg/kg, s.c.), given twice daily with an interdose interval of 4 h, starting on PND 35–60 (Piper and Meyer, 2004). Researchers observed that the repeated MDMA treatment led to an anorectic effect in rats, and at PND 65, rats showed impairments in non-spatial working memory and decreased anxiety-like behaviour. The results suggest that MDMA exposure during adolescence can alter subsequent cognitive and affective function, in the absence of severe damage to the

serotonergic system, since only mild decreases were found in 5-HT binding at PND 70 (Piper and Meyer, 2004). Administration of MDMA also showed the ability to produce deficits in working memory and promote anxiety-related responses in adult rats (Gurtman et al., 2002; Mechan et al., 2002; Morley et al., 2001). Moreover, exposure to MDMA (5, 10, or 20 mg/kg, s.c., twice daily) promoted changes in the learning and memory ability (Broening et al., 2001). Rats exposed to MDMA during the period PND 11–20 revealed impairments in the sequential learning on PND 59–68, and in the spatial learning and memory on PND 73–82, although rats exposed on the period PND 1–10 presented no significant changes at adulthood (Broening et al., 2001).

The differences in the administration scheme strongly influence the effects observed after MDMA exposure during adolescence. A study examined in adolescent rats the influence of intermittent administration of MDMA (2×10 mg/kg, s.c., every 5th day from PND 35 to 60, with each dose separated by 4 h) on their behavioural, physiological, and neurochemical responses to a further, at PND 67, MDMA binge (4×5 mg/kg or 4×10 mg/kg, hourly for 4 h) rechallenge or a 5-HT_{1A} receptor agonist challenge [a single dose of 0.1 or 0.5 mg/kg of 8-hydroxy-2-(di-n-propylamino) tetralin] (Piper et al., 2006). The intermittent exposure to MDMA during adolescence attenuated or even prevented some physiological behaviours and neurotoxic responses to the MDMA binge exposure at PND 67. The hyperthermic effects of MDMA were attenuated and the locomotor hypoactivity and 5-HT neurotoxicity were blocked by the intermittent exposure to MDMA during adolescence. MDMA-treated animals also showed an attenuation of 5-HT syndrome response promoted by a high dose of the 5-HT_{1A} receptor agonist. The results suggest that chronic intermittent MDMA exposure during adolescence may induce 5-HT_{1A} receptor desensitization, as well as neuroadaptive changes that can protect against the adverse consequences of a later high-dose MDMA binge rechallenge (Piper et al., 2006).

Meanwhile, in adolescent rats on PND 45 a dose of MDMA (4×10 mg/kg, i.p., every 2 h), induced hyperthermia in the day of the experiment and, two weeks after the exposure, researchers observed lipid and protein peroxidation, mitochondrial DNA deletion and subsequently impaired expression of subunits of the mitochondrial complexes I (NADH dehydrogenase) and IV (cytochrome c oxidase). These are essential complexes of the mitochondrial respiratory system and are required for energy production. Therefore these alterations promoted by MDMA may cause long-term impairment in brain's mitochondria (Alves et al., 2007). Rats pre-treated with selegiline (2 mg/kg, i.p.), a MAO-B inhibitor, had no changes in the hyperthermic response promoted by MDMA, but selegiline counteracted the oxidative stress effects induced to mitochondria in the mentioned MDMA regimen. Authors suggested that monoamine oxidation by MAO-B may play an important role in the neurotoxicity induced by this amphetamine (Alves et al., 2007).

Repeated intermittent MDMA binges (3×5 mg/kg, i.p., given 3 h apart, every 7th day for four weeks) were administered to adolescent rats and mice aged seven weeks (Kindlundh-Högberg et al., 2007). In rats and mice, the total horizontal activity was significantly increased after the first and third weeks of MDMA binge exposure. The repeated intermittent administration of MDMA to rats promoted a significant down-regulation of 5-HTT density in the nucleus accumbens' shell. In contrast, in mice the same treatment produced a significant down-regulation of DAT in the caudate putamen and nucleus accumbens' shell, and no changes in 5-HTT density. These results showed that the long-term intermittent administration of MDMA to adolescent rats and mice produced differential regulation of 5-HTT and DAT densities (Kindlundh-Högberg et al., 2007).

Repeated and intermittent administration of MDMA (5 or 10 mg/kg, i.p., for three days) was given to mice at different periods of development, particularly at early (28 days old), middle (38 days old), or late (52 days old) adolescence and the carryover effects of this treatment were investigated in the adulthood (80 days old) (Morley-Fletcher et al., 2002). The referred treatment with MDMA, mainly at early and middle adolescence, produced long-term increases in social interaction and environment exploratory activity, and no changes in the animals' aggressive behaviour. MDMA administration also produced long-term reduction in hypothalamic 5-HT levels, accompanied with a marked reduction on the 5-HT concentration, in mice treated at early and middle adolescence. Moreover, a rechallenge with MDMA (5 mg/kg, i.p.) at adulthood, after a previous exposure to MDMA during adolescence, induced hyperactivity in all groups, and increased hypothalamic levels of 5-HT and reduced hypothalamic levels of 5-HIAA in all groups. These results suggest that the long-lasting behavioural and neurotoxic effects promoted by MDMA are dependent on the developmental stage at exposure to the drug (Morley-Fletcher et al., 2002).

A recent study examined the effects of repeated administration of MDMA (5 or 10 mg/kg, i.p., once daily for four days) to rats during late adolescence (PND 38–41) on place conditioning, anxiety behaviour, and monoamine levels (Cox et al., 2014). The treatment with 5 mg/kg of MDMA had no effect on any of the studied parameters. However, the 10 mg/kg MDMA treatment during adolescence caused place aversion one day after the last exposure to the drug, avoidance behaviours in the light–dark box, and also increased anxiety-like behaviours in the open field five days after cessation of MDMA. On the other hand, the same dose of 10 mg/kg produced no changes in monoamine levels in the hippocampus, but decreased 5-HT levels in the dorsal raphe, and increased 5-HT and 5-HIAA levels in the amygdala five days after the last MDMA administration. These data imply that the production of anxiety-like behaviours is related with a more complex mechanism associated with regionally-distinct deregulation of the 5-HT system. In addition, data also suggest that more studies are necessary to assess the mechanism that leads to this regionally-distinct neuroplastic changes in the monoamine system that are accompanied with modified behaviour (Cox et al., 2014).

A recent study was performed in rats to evaluate the effects of MDMA on 5-HTT densities in the frontal cortex and midbrain using single photon emission computed tomography (SPECT) with the 5-HTT ligand, ^{123}I-labelled 2b-carbomethoxy-3b-(4-iodophenyl) tropane ([^{123}I]-β-CIT) (Klomp et al., 2012). Authors aimed to access whether MDMA effects in 5-HTT densities were dependent on the age of first exposure. Therefore, they administered MDMA (10 mg/kg, s.c., twice daily for four days) to adolescent rats at PND 27 and to adult rats at PND 63 (+/− five days). The 5-HTT densities were evaluated eleven days after the last MDMA treatment, at PND 38 in early-exposed (adolescent) rats and at PND 74 (+/− five days) in late-exposed (adult) rats. This MDMA treatment produced significant reductions in 5-HTT binding in several brain regions, which were less pronounced in adolescent rats (ranging from 20% to 69%) when compared to adult rats (ranging from 35% to 75%). The effect of age and treatment was observed in the frontal cortex of rats and not in the midbrain (probably due to an early maturation of the midbrain in rats). The degree of 5-HTT loss in adolescent rats (35%) was less extensive when compared to adult rats (49%) after MDMA treatment, presumably because 5-HTT increases with the increasing age ([^{123}I]-β-CIT binding ratios in the prefrontal cortex of control adult rats were 21% higher when compared to adolescent control rats). Researchers concluded that the differences on MDMA effects on the developing and mature brain might be due to differential maturational stages of the 5-HT projections at age of first exposure (Klomp et al., 2012).

In order to assess the importance of MDMA chirality in its behavioural effects, researchers treated adolescent (32 days old) rats with 5 or 10 mg/kg of RS-MDMA or with 5 mg/kg of each one

of its enantiomers, R- and S-MDMA, during two treatment stages (stage one: days 1–10; stage two: days 15, 17, 19, s.c., once per day). All the animals were also rechallenged with 5 mg/kg of S-MDMA on day 31 and with 10 mg/kg of RS-MDMA on day 33 (Von Ameln and Ameln-Mayerhofer, 2010). The treatment with R-MDMA failed to produce hyperactivating effects, but instead caused decreased locomotor behaviour. On the other hand, RS-MDMA or S-MDMA generated a massive hyperlocomotion and led to the development of behavioural sensitization. When R- and S-MDMA were administered together, researchers observed an increasing in hyperactivity and behavioural sensitization induced by S-MDMA, and the animals pre-treated with R-MDMA showed a sensitized response after the rechallenge with RS-MDMA in adulthood. Taken together, these findings suggest that both MDMA enantiomers can induce behavioural changes after repeated administration during adolescence, and that the sensitization development is more pronounced with S- and RS-MDMA (Von Ameln and Ameln-Mayerhofer, 2010).

MDMA-induced neurotoxicity to the serotonergic terminals is absent during gestational or in the immediate perinatal period, being the onset of neuronal susceptibility to this drug placed between PND 28 and PND 35. Moreover, susceptibility of the serotonergic system is markedly increased when exposure to MDMA occurs in adulthood, when compared to the exposure in adolescence or in the perinatal period. Regardless, MDMA promotes long-term decreases in the levels of 5-HT, 5-HIAA and also in 5-HTT binding sites when administered during adolescence. Adolescent animals' exposure to MDMA can also affect their cognitive function in the absence of evident damage to the serotonergic system. Animals exposed to MDMA in the immediate perinatal period present no significant changes in learning and memory in adulthood, in contrast to MDMA-exposure in older animals. The long-lasting behavioural and neurotoxic effects promoted by MDMA are dependent on the developmental stage of exposure to the drug, possibly due to the differential maturational stages of the 5-HT projections at age of first exposure. However, there is a lack of studies that compare the effects of equivalent treatment regimens under identical conditions at differential stages of development. Altogether, these studies may suggest that younger animals are more resistant to MDMA immediate neuronal damage, although long-term effects are still scarcely investigated. Furthermore, adolescent animals are vulnerable to MDMA neurotoxicity and the use of this amphetamine can severely influence their normal neurotransmitter functions, and consequently induce changes in behaviour and neurotoxicity markers. At this point, mainly the serotoninergic function has been intensely investigated, meaning that more broad studies on MDMA-induced neurotoxicity are needed. The neurotoxic doses of MDMA in the neonatal and adolescent rat developmental stages are represented in Fig. 4.

4.3. Methamphetamine

Like other amphetamines, METH is also widely used by adolescents, and therefore is extremely important to understand its neurotoxic potential during this developmental period. METH administration might result in neurotoxicity, which can be characterized biochemically by depletion of DA, 5-HT, along with an increase in the expression of glial fibrillary acidic protein (GFAP). Moreover, neurotoxicity seems to be increased by the hyperthermic response (Cappon et al., 1997). A single METH dose (10 mg/kg, s.c.) was given to developing rats at PND 20, 40, or 60 at ambient temperatures of 22 °C or 30 °C. The drug administration to PND 60 rats at 22 °C induced animal hyperthermia and resulted in a 47% decrease of neostriatal DA, and 49% increase in the GFAP content, while administration to PND 40 rats at the same ambient temperature failed to induce a hyperthermic response and no changes in DA or GFAP were reported. Interestingly, when administered to PND 40 rats at an ambient temperature of 30 °C, METH induced hyperthermia, and resulted in a 54% reduction of neostriatal DA and a 70% increase in GFAP. Moreover, METH administration at PND 20 did not cause DA depletion or increases in GFAP, at either ambient temperature. These data showed that hyperthermia is necessary to develop neurotoxicity at PND 40, while at PND 20 the rats seem resistant to the neurotoxic effects induced by METH. Altogether, these data suggest that the rat neostriatal susceptibility to this drug may start at approximately PND 40 and the younger animals (20-day-old) are less susceptible to the neurotoxic effects of METH (Cappon et al., 1997).

Another study performed in rats examined the response of the monoaminergic system in adolescent (PND 40) and adult (PND 90) animals when subjected to a high dose regimen of METH (10 mg/kg, s.c., four injections, 2 h apart) (Kokoshka et al., 2000). This treatment did not evoke death in younger rats, but led to a 20% mortality rate within the older group at PND 90. The treatment with METH produced long-term (seven days after the treatment) decreases of 33–53% in DAT activity, tyrosine hydroxylase (TH) activity, and DAT ligand binding in the striatum of PND 90 rats when compared to control rats, although these deficits were absent in PND 40 animals. In fact, 1 h after the treatment, DAT activity was already decreased at PND 90. In contrast, the PND 40 group only showed a transient decrease in striatal DAT activity at 1 h, which returned to the control levels at seven days. Moreover, to examine the effects of METH to the serotonergic systems, researchers also measured the long-term (seven days) and acute (1 h) responses induced by this drug to TPH activity, and observed reduced striatal TPH activity in both PND 40 and 90 animals. Age-dependent differences in the concentration of METH in the striatum and plasma 1 h after the drug administrations were seen, with PND 90 having the double concentration of METH when compared to PND 40 rats. These data clearly showed an age-dependent difference in the long-term dopaminergic depletion seen after METH exposure, which might also be related to the age differences in METH pharmacokinetics. However, the serotoninergic system seems equally sensitive in both populations (Kokoshka et al., 2000).

The tolerance of adolescent rats to the neurotoxicity of METH is an important matter regarding the neurotoxicity towards adolescent animals. A binge treatment of METH (10 mg/kg, s.c., four injections, 2 h apart) was administered to adolescent (PND 40) and adult (PND 90) rats to assess the long-term effects (seven days after) of the drug on the DA system (Riddle et al., 2002). METH treatment promoted an hyperthermic response in adult rats but not in adolescents. Seven days after the METH binge exposure, the striatal DA uptake and DAT ligand binding were significant decreased in adult rats, but no changes were observed in the adolescent animals. The same study reported that when animals received a biweekly pre-treatment with METH (15 mg/kg, s.c., single dose, two consecutive days, for six weeks) starting on PND 40, and one week after the treatment (PND 90) were exposed to the METH binge treatment (4×10 mg/kg, s.c., 2 h apart), no DA deficits were observed. The decreases in striatal DA uptake and DAT ligand binding, seven days after the METH binge exposure, were prevented by the pre-treatment with METH during adolescence. Moreover, the biweekly pre-treatment with METH also attenuated the acute hyperthermia observed in PND 90 rats after the exposure to the binge treatment. In order to ascertain the contribution of putative pharmacokinetic differences to the neuroprotection observed by the biweekly METH pre-treatment, the striatal and whole brain concentrations of METH were assessed. No differences were observed and the levels of METH 1 h after the binge exposure were similar between adult animals that received and did not received the METH pre-treatment. Taken together, these findings indicate that the observed neuroprotection was not a result of pharmacokinetic tolerance, but it was

possibly a result of the attenuation of the hyperthermic response (Riddle et al., 2002).

The acute (1 h) and long-term (seven days) effect of multiple administrations of METH on VMAT2 was studied in adolescent (PND 40) and adult (PND 90) rats (Rau et al., 2006; Truong et al., 2005). Different METH regimens were administered to the two groups of animals. To examine the acute effects of METH, adult rats received 4 × 5 mg/kg (s.c., 2 h apart) of METH producing brain METH concentrations of 4.31 ± 0.49 ng/mg 1 h after the treatment, while adolescent animals received 4 × 10 mg/kg (s.c., 2 h apart) or 4 × 15 mg/kg (s.c., 2 h apart) producing brain METH concentrations of 5.03 ± 0.38 ng/mg or 10.70 ± 1.15 ng/mg, respectively, 1 h after the treatment. The obtained data revealed that adult rats presented a 65% decrease in vesicular DA uptake, 1 h after the treatment with METH. Meanwhile, the dose administered to the adolescent animals that allowed comparable brain METH concentrations (4 × 10 mg/kg, s.c., 2 h apart) led to a 45% decrease in vesicular DA uptake 1 h after METH. No further decrease in the vesicular DA uptake was seen 1 h after the higher METH dose administered to the adolescent animals (Rau et al., 2006; Truong et al., 2005). Importantly, higher basal levels of VMAT2 immunoreactivity and vesicular DA uptake were observed in the adult animals when compared to adolescents, possibly contributing to the greater neurotoxic effect of METH in the older group. Moreover, the long-term consequences of METH were assessed, and adult rats received 4 × 5 mg/kg (s.c., 2 h apart) or 4 × 10 mg/kg (s.c., 2 h apart) and adolescents received 4 × 10 mg/kg (s.c., 2 h apart) of METH and animals were sacrificed seven days after METH administration. METH treatment led to significant decreases in striatal DA content and vesicular DA uptake in PND 90 rats, but had no effect on those parameters on PND 40 animals, seven days after the METH administration. Importantly, the basal striatal DA content was also higher in adult animals when compared to adolescents (Rau et al., 2006; Truong et al., 2005). These results show that differential age-related responses to METH exposure may be a result of (1) differences in the pharmacokinetic METH disposition; (2) differential basal levels of VMAT2 immunoreactivity and vesicular DA uptake in adult *versus* adolescent animals; and (3) higher levels of basal striatal DA content in adult *versus* adolescent animals. Altogether, these factors may contribute to the resistance of adolescent rats towards METH and for the increase vulnerability of the dopaminergic system to the long-term effects of METH in older animals (Rau et al., 2006; Truong et al., 2005).

In order to ascertain the factors that determine the resistance of adolescent rats towards METH neurotoxicity and the vulnerability of adult rats to the METH-induced deficits, another study performed experiments concerning the age-related differences in monoamine transporter function using rat striatal suspensions obtained from untreated and unanesthetized male adolescent (PND 38–42) and adult (PND 88–92) rats (Volz et al., 2009). Using this *in vitro* system, results showed that the initial velocities of inwardly DA transport into and outwardly METH-induced DA efflux from striatal suspensions are higher in adolescent animals than in adults. The western blot analysis demonstrated a greater DAT immunoreactivity in striatal suspensions obtained from adolescent rats when compared to adults. The initial velocities of inwardly VMAT2-mediated DA transport into membrane-associated vesicles were higher in adolescent rats when compared to adults. However, no differences were found in VMAT2 immunoreactivity in membrane-associated vesicles between the two groups. The increased vesicular DA transport velocities and the absence of differences in VMAT2 immunoreactivity in adolescent rats implies that VMAT2 is kinetically upregulated in the membrane-associated vesicles, therefore, the vesicles of younger animals have higher ability to sequester cytoplasmic DA than adults. Besides, the adolescents presented higher functionally active DAT levels, having more efflux pathways for METH-promoted DA release from the vesicles into the cytoplasm. These facts may prevent the elevation of cytoplasmic concentrations of DA into neurotoxic levels after a binge administration of METH in adolescent animals, being a possible explanation for the resistance of younger animals to the drug (Volz et al., 2009).

In mice, METH also induces age-related different responses in terms of dopaminergic neurotoxicity. The neurotoxic regimen of METH (4 × 10 mg/kg, s.c., every 2 h) produced minimal and non-persistent depletion of DA and its metabolites in 1-month-old mice, while mice of 12 months of age suffered large and persistent depletions of DA (87%), DOPAC (71%), and homovanillic acid (HVA) (94%) in the striatum (Miller et al., 2000). This METH regimen was also minimally effective in inducing elevations of GFAP in 1-month-old mice, when compared to the large elevations in striatal GFAP in mice of 2, 5, 12, or 23 months of age. Moreover, with increasing dosages of METH (4 × 20 mg/kg, 4 × 40 mg/kg or 4 × 80 mg/kg, s.c., every 2 h) the response of GFAP increased by 100% over control in 1-month-old mice, but it still remained extremely below the levels of increase reported in mice with 12 and 23 months of age (300–400% over control). These results also suggest that younger animals are less susceptible to the neurotoxic damage induced by METH, and this neurotoxicity might be dependent on the maturity of the striatal DA systems (Miller et al., 2000).

In another study, METH (0, 5, 10, 20, and 40 mg/kg, i.p., single dose) was administered to rats of 1, 6, or 12 months. The administration of 40 mg/kg METH resulted on 100% mortality in 12-month-old animals (Imam and Ali, 2001). In the striatum of 1-month-old rats after 5 mg/kg METH dose there was no formation of 3-nitrotyrosine, indicating no formation of peroxynitrite, and no dopaminergic alterations. However, at this age the administration of 10, 20, and 40 mg/kg METH produced a significant dose-dependent increase in 3-nitrotyrosine and dose-dependent depletions of DA and its metabolites, DOPAC and HVA, when compared to the paired control group. In the 6-month-old rats, all METH doses (5, 10, 20, or 40 mg/kg, i.p.) produced a significant increase in 3-nitrotyrosine formation in a dose-dependent manner and the levels were also higher when compared to those of 1-month-old rats. In this age, rats also reported dose-dependent depletions in the levels of DA and its metabolites, in all dosages used. Moreover, a single injection of METH (5, 10, or 20 mg/kg, i.p.) also resulted in a significant dose-dependent formation of striatal 3-nitrotyrosine on 12-month-old rats, which was significantly higher when compared to the other two younger groups tested. In this group, a significant dose-dependent depletion of DA, DOPAC, and HVA levels also occurred and dopaminergic neurotoxicity was more pronounced when comparing to the 1-month-old or 6-month-old METH-treated rats. Moreover, an age-dependent increase in the hyperthermic response was also reported after METH administration. Hence, these results suggest, once again, that aging increases the susceptibility of animals to the neurotoxicity of METH (Imam and Ali, 2001).

A study performed in rats used a biweekly treatment with METH (7.5 mg/kg on two consecutive days, s.c., for six weeks) that started in adolescence (PND 40) or a binge treatment (4 × 7.5 mg/kg, 2 h apart, s.c.) in adulthood (PND 90) (McFadden et al., 2011). The drug treatment during adolescence had no effects, in contrast to the binge treatment at PND 90 that caused acute and persistent deficits in VMAT2 function. However, the biweekly treatment during adolescence prevented the acute and persistent deficits in VMAT2 function and the acute hyperthermic response, caused by the subsequent METH rechallenge (4 × 7.5 mg/kg, 2 h apart, s.c.) in adulthood at an ambient temperature of 23 °C. Nevertheless, when the rechallenge was administered at a higher ambient temperature (25 °C), the hyperthermia was maintained and the referred protection produced by the biweekly treatment during adolescence was abolished (McFadden et al., 2011).

Another study tested the dose-response to successive ten-day intervals of METH exposure in rats within the periods PND 21–30, PND 31–40, PND 41–50, or PND 51–60 (Vorhees et al., 2005). Several METH doses were tested in each group of animals. Some METH regimens failed to produce changes in the spatial learning/reference memory and sequential learning, namely on PND 21–30 (regimens used in the group: 2.5, 5, or 10 mg/kg/dose × 4 dose/day, s.c.), PND 31–40 (regimens used in the group: 1.25, 2.5, 5, or 7.5 mg/kg/dose × 4 dose/day, s.c.), or PND 51–60 (regimens used in the group: 1.25, 2.5, 3.75, or 5 mg/kg/dose × 4 dose/day, s.c.). However, impairments in spatial learning/reference memory and sequential learning were seen after treatment with the highest dose (6.25 mg/kg/dose, s.c.) on PND 41–50 (regimens used in the group: 1.25, 2.5, 5, or 6.25 mg/kg/dose × 4 dose/day, s.c.). The effects observed at PND 41–50, which refers to the adolescent stage of brain development in rodents, suggests that, at this age, there is a superior susceptibility of rats to cognitive deficits induced by METH when compared to juvenile (PND 21–30, PND 31–40) or adult rats (PND 51–60) (Vorhees et al., 2005).

A study in adolescent mice (28–42 days old) with exposure to a repeated neurotoxic regimen of METH (24 mg/kg, i.p., once daily, for 14 days) was conducted to ascertain if METH exposure promoted changes in hippocampal plasticity or short-term memory (North et al., 2013). Researchers observed that after 14 days of METH exposure there were no deleterious consequences on short-term memory or hippocampal neurotransmission. However, after a period of 21 days of drug abstinence, they found deficits in spatial memory and decreases in hippocampal plasticity. Authors concluded that the deleterious consequences on short-term memory and hippocampal neurotransmission induced by a neurotoxic regimen of METH may manifest and persist after an abstinence period (North et al., 2013).

Age-dependent differences in the long-term dopaminergic neurotoxicity are seen after METH exposure. Perinatal and adolescent animals are more resistant to the neurotoxic effects of METH to the dopaminergic system, with the onset of susceptibility to this drug placed after PND 30. Pharmacokinetic differences in METH disposition among adolescent and adult animals seem to be contributors for the age-dependent differences in METH toxicity. More importantly, the differences in the dopaminergic neurons among adolescent and adult animals may be crucial in the response towards METH. While older animals have higher levels of DA in the striatum, adolescents present a kinetically up regulated VMAT2 and the vesicles have higher ability to sequester cytoplasmic DA. Therefore, adolescents show a greater ability to prevent the elevation of cytoplasmic concentrations of DA after METH exposure, which results into neurotoxic levels. Therefore, the lower susceptibility to the neurotoxicity of METH in adolescent rats is possibly a result of differential stages of development of the dopaminergic system. Like for the other two amphetamines, there is a lack of studies comparing the effects of equivalent treatment regimens under identical conditions at differential stages of maturity. Hence the susceptibility of animals to the neurotoxic effects increase with the animal age. However, the late consequences of adolescent exposure to METH are poorly assessed. The neurotoxic doses of METH in adolescent rat developmental stages are represented in Fig. 5.

5. Neurotoxicity to young humans that consumed amphetamines

It is difficult to extrapolate the results obtained in animal experimentation to humans, being extremely important to confirm the ATS neurotoxicity demonstrated in laboratory animals with observational studies conducted in human subjects. Studies with human adolescents have some ethical barriers, due to their age, thus, they are frequently not enrolled in studies to evaluate the drug abuse consequences (King et al., 2010). Studies with human drug users raise a series of challenges regarding data interpretation, and also ethical barriers. First of all, most individuals are polydrug users and buy drugs of unknown purity and content rendering uncertain the exact amount of drug exposure. Thus, it is hard to ascertain whether a sole drug or the mixture might be the cause of toxic effects (Cole and Sumnall, 2003; Jager et al., 2007). Additionally, potentially pre-existing brain diseases, gender, and genetic differences may influence the consequences of exposure to the mentioned drugs. Studies in humans are retrospective the influence of these factors may be uncertain (Liechti et al., 2001; Segura et al., 2005). Despite the fact that most reports consistently report neurotoxic effects in former human drug users, these brain changes are viewed by some as neuroadaptations and could be reversible (Seger, 2010). Bearing in mind the inherent limitations of conducting studies with humans, they are of extreme importance to confirm the findings of studies conducted in laboratory animals, and to disclose the human brain associated changes related to drug misuse under the real scenario of consumption. The studies on the long-term effects of drugs to the humans' brain are based on the measurement of neurotransmitter metabolites in the cerebrospinal fluid or in neuroimaging data. The data of most studies described herein were obtained by neuroimaging studies, such as, magnetic resonance imaging, positron emission tomographic studies, SPECT, transcranial sonography, and neuropsychological tests. With the notable exception of post-mortem studies conducted in former drug users, where direct neuronal damage assessments can be made, measurements in human abusers must be indirect. Importantly, studies performed in young adults are necessary to assess the effects of amphetamines at this developmental stage, since young people extensively consume these psychoactive drugs. Also, the assessment of the neurotoxicity in young adults that were previous consumers in adolescence can warrant important data.

5.1. Amphetamine

As previously mentioned, AMPH is not only a recreational drug, since it is also used for ADHD therapy in children and adolescents. For that reason, researchers have shown concerns for the possible neurotoxic effects of this drug. Unfortunately, the adolescent human population is understudied, also due to ethical issues. Several investigators evaluate the late consequences of possible exposure to the drug during adolescence in people more than 18 years old (Reske et al., 2010; Willson et al., 2004). Below are reviewed the few studies conducted mostly in young adults to evaluate the neurotoxic consequences of AMPH.

Reske et al. performed a study in non-dependent stimulant users, with ages between 18 and 25 years that used AMPH and methylphenidate at least for the past six months, to assess the behaviour and brain functioning under the occasional use of these drugs. It was observed that an increased use of AMPH and methylphenidate was associated with strong verbal memory and learning deficits. Also, the learning and memory problems were present in individuals with a minimal use of stimulants, leading to possible pre-existing neurocognitive impairments in the studied population. Even so, they concluded that the prescription of AMPH and methylphenidate may lead to an intensification of these deficits (Reske et al., 2010).

A paper reported the AMPH effects on motor and verbal skills, memory, and spatial attention task in 18 healthy volunteers (with an average age of 25.4 ± 6.51 years) with the help of functional magnetic resonance imaging (fMRI). In that study, a single oral dose of 25 mg d-AMPH caused decreases in the activity of several brain regions during cognitive tasks. These effects may be linked to the behavioural changes observed after the AMPH administration, and

are possibly mediated by alterations in dopaminergic activation (Willson et al., 2004).

5.2. "Ecstasy"

"Ecstasy" is also widely used by young humans, and is extremely important to study the neurotoxic effects in MDMA users. A fMRI study on 33 heavy MDMA users (mean use of 322 pills) with a mean age of 23 ± 3.8 years, evaluated the effects of "ecstasy" on working memory, attention, and associative memory. The results showed that the use of this drug had no effects on working memory and attention, but was associated with reduced memory performance. Memory performance is apparently more affected by AMPH than by MDMA in humans (Jager et al., 2007). Several studies reported a decreased density in 5-HT neurons, with reduced 5-HTT binding sites in young adult MDMA users (McCann et al., 1998, 2005, 2008). Brain 5-HTT density is related with memory performance, suggesting that the observed deficits in 5-HTT will be related with the deficits in memory seen in humans with an history of MDMA abuse (McCann et al., 2008). An investigation conducted in 49 chronic "ecstasy" users (with an average age of 25.9 ± 0.8 years and an average MDMA use of 4.1 ± 0.4 years, typically one to two tablets bi-monthly), reported a significant decrease in 5-HTT binding in cerebral cortex (19–46% loss of 5-HTT), and hippocampus (21% loss of 5-HTT) (Kish et al., 2010). Those effects were related with the years of drug use. Moreover, the MDMA users reported subnormal mood and deficits in some attention tests, executive function and memory, and the memory deficits were correlated with the decreased 5-HTT binding sites (Kish et al., 2010), which corroborates the previous study from McCann et al. (2008). In another study performed in MDMA users (with an average age of 26.23 ± 1.99 years and an average MDMA use of 4.52 ± 0.71 years), it was observed that this drug decreased the levels of 5-HT metabolite, 5-HIAA, in the cerebrospinal fluid. Moreover, it was stated that the brain 5-HT injury might be related with cognitive deficits, since the MDMA users revealed performance deficits on several tasks, namely sustained attention task requiring arithmetic calculations, a task that required complex attention and incidental learning, a task requiring short-term memory, and a task of semantic recognition and verbal reasoning (McCann et al., 1999). Other studies also reported possible 5-HT neurotoxicity, which was related with evidences of cortical hyper-excitability and chronic alterations in cortical 5-HT signalling in MDMA users, aged between 18 and 35 years old (Bauernfeind et al., 2011; Di Iorio et al., 2012).

A recent study was performed in adolescents (14–18 years) and young adults (18–36 years) to evaluate the effects of MDMA on brain 5-HTT densities in the frontal cortex and midbrain using SPECT and the 5-HTT ligand, [^{123}I]-β-CIT (Klomp et al., 2012). The MDMA users were stratified in two different groups: group one with ages between 14 and 18 years, representing the early-exposed group (developing brain), and group two with ages between 18 and 36 years, representing the late-exposed users (mature brain). On average, five years after the first exposure, researchers reported that early age of first exposure accounted for a notable 79% of midbrain 5-HTT density variability in the developing human brain, in contrast to 0.3% variability in late-exposed users. No relationship among age of first MDMA exposure and 5-HTT binding was observed in the frontal cortex. It was concluded that the differential effects of MDMA on the developing and mature brain might be due to differential maturational stages of the 5-HT projections at age of first exposure (Klomp et al., 2012).

A study conducted with 31 polydrug users that used MDMA (average age of 21.7 ± 3.3 years old and abstinent from MDMA at least three weeks before starting the study) *versus* 29 non-MDMA users with history of abuse of other substances (average age of 24.3 ± 3.5 years old) compared brain grey and white matter concentration. The researchers observed that MDMA users had decreased grey matter concentration in several brain regions (neocortical, bilateral cerebellum, and midline brainstem) (Cowan et al., 2003). With the aim of assessing the sustained effects of "ecstasy" on the brain, another group performed a study in abstinent novel "ecstasy" users (low-dose MDMA users) with a combination of neuroimaging techniques. The researchers used young adults with a mean age of 21.7 ± 3.0 years that consumed, on average, six tablets in 20.3 ± 23.8 weeks. They observed that novel users, even in low doses of the drug, showed signs of brain damage, such as vasoconstriction and axonal damage (de Win et al., 2008).

Flavel et al. performed a study in MDMA abstinent users for an average of three months, with an average age of 22 ± 3 years old, to assess the late effects of this stimulant on human tremor during rest and movement. The MDMA users presented an abnormal large tremor during movement, even with a minimal to moderate lifetime use of MDMA (subjects that used MDMA on less than 20 occasions) and had been abstinent for an average of three months. These data do not seem related to any acute mechanism of action of the drug. The authors stated that these abnormalities may account for a possible risk for movement disorders in MDMA users (Flavel et al., 2012). The same group reported abnormal substantia nigra morphology in abstinent illicit stimulant (AMPH, MDMA, METH, and cocaine) users with an average age of 31 ± 9 years. These deficits in nigro-striatal system raised some concerns, giving the high risk for a later development of Parkinson's disease (Todd et al., 2013).

The evaluation of former (even abstinent) MDMA use during adolescence demonstrates that this drug may affect neurotransmitter function and reduce memory performance in young adults. Moreover, data show that the distinct maturational brain stages may have an important role in the impact of long-term consequences of "ecstasy" use.

5.3. Methamphetamine

Like other amphetamines, METH is also widely abused by humans and it's extremely important to assess the neurotoxic actions of METH in the human brain. McKetin et al. performed a study with 309 METH users with ages ranging from 16 to 60 years old being the median age of first use of the drug 17 years old. They observed that 30% of the participants were screened positive for psychosis in that year. That leads to the thought that chronic use of METH might be associated with the development of paranoid psychosis (McKetin et al., 2006).

A study involving 54 adolescent METH users and 74 control subjects, with ages ranging from 12 to 23 years old, assessed the neuropsychological performance of these adolescents after exposure to METH (an average use of 0.58 ± 0.08 g per day in males and 1.02 ± 0.22 g per day in females). All subjects were submitted to several neuropsychological tests and the METH users presented impairments in memory and executive function. Moreover, these impairments appear to be attenuated by a prolonged abstinence to the drug. Researchers concluded that the use of METH is associated with cognitive deficits (King et al., 2010).

A study with 34 METH-dependent adults with an average age of 33.1 ± 8.9 years (population generally used the drug for ten years, in a frequency superior to five times per week, and abstinent for 18 days) and 31 healthy non-METH user subjects with an average age of 35.7 ± 8.4 years, measured the grey matter volumes in the both groups. METH users showed an age-dependent loss of cortical grey matter in frontal, occipital, temporal, and the insular lobes when compared to control subjects, and smaller grey matter volumes in several brain subregions. The authors concluded that METH users increased their grey matter loss with age, raising the possibility of accelerated decline in mental function (Nakama et al.,

2011). Other studies also corroborate that METH abusers present grey matter deficits, a marker of neurotoxicity (Schwartz et al., 2010; Thompson et al., 2004). Researchers pointed that METH users, which used the drug for an average of 10.5 years starting at their mid-twenties, had 7.8% smaller hippocampal volumes than control subjects and that data were associated with impaired memory performance. They also reported a significant white matter hypertrophy of 7.0%, accompanied with damage in the medial temporal lobe and in the cingulated-limbic cortex in METH users. Altogether, these indications of cerebral deterioration caused by chronic METH use can lead to impairments of memory performance (Thompson et al., 2004). Other authors reported that the use of drugs in a juvenile age (subjects that initiated the drug use before 21 years old) was related with smaller intracranial volume (Schwartz et al., 2010).

Regarding METH use in adolescence, studies show evidences of long-term neurotoxicity, such as, grey matter loss, development of paranoid psychosis, cognitive deficits, and impaired memory performance.

6. Future perspectives on the field

Despite decades of research with amphetamines, many issues remain unsolved and many questions are still presently unanswered. It seems unequivocal that ATS are neurotoxic to laboratory animals. Nonetheless some authors claim that the reported brain changes, including the decrease in biochemical monoaminergic systems, can represent neuroadaptations to drug exposure. Besides, the reported brain changes and the neurotoxic mechanisms of amphetamines have not yet been fully explained. Many studies remain to be done, and that data are of extreme importance given that ATS are not only drugs of abuse, but they are used therapeutically in ADHD and several other disorders.

Manny laboratories report that exposure to ATS during the adolescence period in experimental animals induces brain changes and promotes neurotoxicity. Reports agree that ATS promote differential effects in animals with different ages. It will be however necessary to promote more research to fully disclose the differential effects of ATS to adolescent animals versus adult ones, which are more prone to neurotoxic events. There seem to be various factors contributing to the lower susceptibility of adolescent animals to the neurotoxicity of ATS, in particular (1) the maturation stages of the brain and monoaminergic neurons at the age of exposure, which may allow neuroadaptation; (2) pharmacokinetic dissimilarities; (3) and the hyperthermic response mechanisms.

Reports seem to agree that the age of exposure to ATS is vital for the outcome. Neonatal animals seem resistant to the neurotoxic effects; meanwhile early adolescent animals may already present neurotoxicity following ATS exposure. Certainly, the stage of brain maturity of the animal will determine the outcome of the exposure. For instance, regarding the dopaminergic system there are important differences among adolescent and adult animals. In adolescent rats, VMAT2 is kinetically upregulated and the vesicles of younger animals have higher ability to sequester cytoplasmic DA than adults. Moreover, adolescents present higher functionally active DAT levels and lower levels of DA in certain brain areas. The higher ability to prevent the elevation of cytoplasmic concentrations of DA into neurotoxic levels may be the key for a lower susceptibility of adolescents to the neurotoxic actions of ATS. Regarding serotonergic neurons, there are differential maturation stages across the brain areas, ruling for diverse responses of those brain areas. This implies the need of the monoaminergic systems to reach a certain stage of maturity to allow the neurotoxic outcome.

Next, several reports have shown pharmacokinetic dissimilarities among adolescent and adult animals: it is necessary to increase the dose in adolescents to attain similar drug brain concentrations that are found in the adults. During the neonatal and adolescent periods, the metabolic systems are still developing and present important differences towards adults that can contribute for lower susceptibility to the drugs. For instance, in the case of MDMA it has been proven that hepatic metabolism is an important contributor for the production of neurotoxic metabolites (Capela et al., 2009). The pharmacokinetic differences explain study designs that use different dose regimens in adolescent animals, and not directly those used in adult animals, as to assure similar brain drug concentrations.

Another issue that seems to be important for a neurotoxic outcome in adolescent animals is the hyperthermic response following the ATS. Not all ages of animals show an hyperthermic response following a dose regimen that in an adult would evoke significant hyperthermia. The mechanisms behind this dissimilar hyperthermic response need to be clarified by further research.

Taking into account the previous factors, one can easily understand why the vast majority of reports that are designed to study the neurotoxic actions of ATS privilege adult animals, where toxic effects are easily evoked. Unfortunately, there is a lack of studies in animals in the adolescent stage of development.

Another important issue that remains to be clarified is how exposure during adolescence may influence animals' brain maturation and behaviour in the future. Several studies report that previous exposure to ATS during the adolescent period may prevent hyperthermia and neurotoxicity in the adulthood following a later challenge with a neurotoxic regimen. This pre-conditioning effect of ATS is still scarcely studied, and their mechanisms may be important to fully understand the neurotoxic actions and therefore develop strategies to prevent neurotoxicity following ATS exposure. Furthermore, it is important to evaluate the role of aging in pre-exposed animals, including the long-term changes in behaviour and brain development following exposure during early ages. Overall, what are the consequences in brain aging after chronic adolescent exposure to ATS?

The translation of animal data to the human situation has always many constraints. It is extremely important to clarify the consequences of AMPH, MDMA, and METH use to the adolescent developing brain, considering that young people all over the world frequently use these drugs. Some studies report neurotoxic consequences of the recreational use of amphetamines in humans, particularly, in young adults, and associated it with behavioural changes, impairments in memory performance and cognitive deficits. Studies in human adolescents are scarce, which might also be due to ethical barriers and confounding factors, as polydrug abuse. Nevertheless, it would be important to bring forward more studies in adolescents for a better understanding how they respond to ATS exposure and to ascertain their long-term consequences.

7. Conclusions

In conclusion, adolescent animals are less susceptible to the neurotoxic effects of amphetamines than adults. The susceptibility to the neurotoxic effects of ATS seems roughly to be located in the early adolescent period of animals. Importantly, neonatal animals are rarely affected by the dose regimens used. As revealed in Figs. 3–5, the majority of the studies conducted in rats to evaluate the neurotoxic action of ATS are placed after the early adolescent period of animals. Many questions are still to be solved by the investigators regarding the differential effects of ATS to the brain and the adult consequences of adolescent exposure to drugs.

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