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Invited review

Psychostimulants and brain dysfunction: A review of the relevant neurotoxic effects

Joana Gonçalves, Sofia Baptista, Ana Paula Silva*

Laboratory of Pharmacology and Experimental Therapeutics, Institute for Biomedical Imaging and Life Sciences (IBILI), Faculty of Medicine, University of Coimbra, Azinhaga Santa Comba, Celas, 3000-548 Coimbra Portugal

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ABSTRACT

Psychostimulants abuse is a major public concern because is associated with serious health complications, including devastating consequences on the central nervous system (CNS). The neurotoxic effects of these drugs have been extensively studied. Nevertheless, numerous questions and uncertainties remain in our understanding of these toxic events. Thus, the purpose of the present manuscript is to review cellular and molecular mechanisms that might be responsible for brain dysfunction induced by psychostimulants. Topics reviewed include some classical aspects of neurotoxicity, such as monoaminergic system and mitochondrial dysfunction, oxidative stress, excitotoxicity and hyperthermia. Moreover, recent literature has suggested new phenomena regarding the toxic effects of psychostimulants. Thus, we also reviewed the impact of these drugs on neuroinflammatory response, blood–brain barrier (BBB) function and neurogenesis. Assessing the relative importance of these mechanisms on psychostimulants-induced brain dysfunction presents an exciting challenge for future research efforts.

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1. Introduction

The abuse of psychostimulants poses a serious international public health concern due to its high potential for addiction and the risk of long-lasting neurological impairment, including the risk of developing Parkinson's disease (Cadet and Krasnova, 2009). The major classical molecular mechanisms by which psychostimulants produce their effects in the brain involves alteration on monoaminergic system, oxidative stress, mitochondrial dysfunction and excitotoxicity. Additionally, emerging aspects, such as neuroinflammation, blood–brain barrier (BBB) function and neurogenesis have been raised as important features of psychostimulants neurotoxicity. Thus, recent mechanisms in combination with the more classic ones will review the negative impact of psychostimulants on brain function. Herein, we will attempt to highlight areas that would benefit from concerted research efforts.

2. Amphetamine and methamphetamine

2.1. Overview of classical aspects of amphetamine and methamphetamine neurotoxicity

2.1.1. Dopamine system dysfunction

The administration of amphetamines compromises dopamine (DA) signalling by the combined actions of vesicular depletion and non-exocytotic efflux (Sulzer et al., 2005). Specifically, these drugs enter DA neurons *via* dopamine transporter (DAT; Cadet and Krasnova, 2009; Carvalho et al., 2012). This will lead to a hyperdopamine state (Willuhn et al., 2010) that includes dysfunction of DAT and/or vesicular monoamine transporter-2 originating an abnormal release of DA (Cadet and Krasnova, 2009; Fleckenstein et al., 2007). Several studies demonstrated that amphetamine (AMPH) and methamphetamine (METH) produce long-term damage in DAergic nerve terminals in multiple brain regions (Booij et al., 2006; Volkow et al., 2001a, 2001b). Indeed, it was observed that a neurotoxic regimen of METH or AMPH increases DA release in rat striatum (Avelar et al., 2013; O'Dell et al., 1993), and decreases DAT, D1 and D2 receptor binding (Booij et al., 2006; Kilbourn and Domino, 2011; Lacan et al., 2013). Moreover, Zhu et al. (2005) reported that a single high dose of METH (30 mg/kg) leads to a

* Corresponding author. Tel.: +351 239480070; fax: +351 239480217.
E-mail address: apmartins@fmed.uc.pt (A.P. Silva).

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depletion of DA terminal markers in mice striatum. Also, D1 or D2 receptor antagonists, SCH23390 or sulpiride, respectively, were able to prevent METH-induced cortical and striatal toxicity, as well as immediate early genes expression, namely Fos (Gross and Marshall, 2009). Importantly, these cellular alterations seem to originate behavioural alterations. Lee et al. (2009) proved that METH-dependent subjects, when compared with healthy control subjects, showed reduced striatal D2/D3 receptor availability, which can be correlated with impulsive temperament. Concerning AMPH abuse, D1-like receptors were shown to be necessary for both behavioural sensitization and locomotor stereotypy (El-Ghundi et al., 2010; Fritts et al., 1997; Karper et al., 2002).

2.1.2. Oxidative stress

It has been shown that amphetamines are potent brain neurotoxins also due to increased production of reactive oxygen and nitrogen species (ROS and RNS, respectively), and lipid peroxidation (Fleckenstein et al., 2007; Yamamoto et al., 2010). In fact, it was verified that both repeated (4× 10 mg/kg, 2 h intervals) and acute (5 and 15 mg/kg) METH treatment result in the formation of lipid and protein markers of oxidative stress in the rat cortex and striatum (Acikgoz et al., 2001) and mouse hippocampus (Gluck et al., 2001). Additionally, human dopaminergic neuroblastoma SH-SY5Y cell line exposed to METH (1.68 mM) showed a decreased mitochondrial membrane potential followed by an up-regulation of ROS levels, which culminated in cell apoptosis (Wu et al., 2007). Moreover, changes in nitric oxide (NO) metabolism can also contribute to METH-induced oxidative stress and neurotoxicity (Itzhak and Ali, 2006). Indeed, both repeated and acute METH administration led to an up-regulation of protein levels of nitrate, 3-nitrotyrosine and neuronal nitric oxide synthase in mice striatum (Anderson and Itzhak, 2006; Wang and Angulo, 2011). The involvement of NO in METH toxicity is also supported by findings that show no formation of 3-nitrotyrosine and DA terminal degeneration in the striatum of neuronal nitric oxide synthase KO mice (Imam et al., 2001). Accordingly, METH neurotoxicity can be attenuated by free radical scavengers and antioxidants (Sharma et al., 2007).

Regarding AMPH, a neurotoxic regimen (7.5 mg/kg), increased the rat striatal levels of 2,3-dihydroxybenzoic acid (index of hydroxyl radical) and malondialdehyde (index of lipid peroxidation), which were accompanied by DA depletion (Wan et al., 2000). Furthermore, other authors reported that, following AMPH chronic treatment, the production of rat cortical and hippocampal thiobarbituric acid reactive substances (Frey et al., 2006a, 2006b) as well as rat hypothalamic superoxide dismutase (Kuo et al., 2009) were increased. Recent pieces of evidence have also suggested that protein kinase C delta (PKCδ) plays a role on AMPH and METH-induced oxidative stress (Kuo et al., 2009; Shin et al., 2012). In fact, depletion of PKCδ gene significantly attenuated the production of lipid peroxidation and protein oxidation in both mice-treated METH (Shin et al., 2012) and rat-treated AMPH (Kuo et al., 2009). The presence of oxidative stress has also been documented in the brain of METH users (Fitzmaurice et al., 2006; Mirecki et al., 2004).

2.1.3. Mitochondrial function

The impairment of mitochondrial function is other important feature of amphetamines neurotoxicity (Krasnova and Cadet, 2009; Yamamoto et al., 2010). In fact, toxic doses of METH inhibited mitochondrial electron transport chain enzyme complex I (Klongpanichapak et al., 2006), complex II/III (Brown et al., 2005) and complex IV (Burrows et al., 2000) in rodent striatum, which was associated with a reduction of adenosine-5′-triphosphate (ATP) stores in the brain (Burrows et al., 2000). More recently, Feier et al. (2012) described that a single administration of AMPH or METH (2 mg/kg each) causes similar impairment of energetic metabolism in rat amygdala, hippocampus, striatum and prefrontal cortex. Specifically, these psychostimulants decreased the activities of Krebs cycle enzymes and mitochondrial respiratory chain enzymes. Moreover, it has been suggested that mitochondria-dependent death pathway has an important role in amphetamines-related neuronal apoptosis (Cadet et al., 2005; Krasnova et al., 2005). In fact, a single high dose of METH (40 mg/kg) caused apoptotic cell death in monoaminergic cells of mice frontal cortex through up-regulation of pro-apoptotic proteins, such as Bax, Bad, Bak and Bid, and reduction of anti-apoptotic molecules, namely Bcl-2, Bcl-X_L and Bclw (Jayanthi et al., 2001). Accordingly, METH induced the release of apoptosis-inducing factor (AIF), Smac/DIABLO and cytochrome *c* from mitochondria into cytoplasmic fractions (Jayanthi et al., 2004). The release of these proteins was followed by activation of caspase-9 and -3 that, in turn, triggered the proteolysis of caspase subtracts, such as Poly (ADP-ribose) polymerase (PARP) or lamin A (Jayanthi et al., 2004; Warren et al., 2005, 2007). Furthermore, repeated AMPH administration (4× 10 mg/kg, every 2 h) induced neuronal apoptosis in the mice striatum *via* mitochondria-depended mechanism that resulted in an early activation of p53, which in turn activated the Bax-dependent caspase pathway (Krasnova et al., 2005). Additionally, our group reported that METH triggers subventricular zone stem/progenitor cell death *via* activation of caspase-3 (Bento et al., 2011). These observations are in agreement with those showing that overexpression of Bcl-2 (Cadet et al., 1997), as well as inhibition of caspases (Uemura et al., 2003) and PARP (Iwashita et al., 2004) can protect against METH-induced cell death.

2.1.4. Excitotoxicity

Several data suggest that glutamatergic system plays an important role in the neurotoxicity induced by psychostimulants, as well as in the development and maintenance of addiction (Kalivas et al., 2009). Indeed, AMPH and METH increase glutamate release in rat striatum (Mark et al., 2007; Reid et al., 1997), hippocampus (Rocher and Gardier, 2001) and ventral tegmental area (Zhang et al., 2001). Moreover, *in vivo* microdialysis studies showed that a neurotoxic regimen of AMPH (30 mg/kg) leads to an increase of glutamine/glutamate ratio in caudate putamen, frontal cortex and hippocampus (Pereira et al., 2008). In addition, both striatal and hippocampal gamma-aminobutyric acid (GABA)/glutamate ratio were increased with the same AMPH regimen (Pereira et al., 2008). Previously, our group observed that an acute METH administration (30 mg/kg) increased the rat striatal and cortical α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor subunit GluR2 protein levels, together with a cortical N-methyl-D-aspartate (NMDA) receptor subunit NR1 and NR2A down- and up-regulation, respectively (Simões et al., 2008). Concerning rat hippocampus, we verified that METH increased GluR2 and NR2A protein levels without changes in NR1 subunit (Simões et al., 2007). These results suggest that the alterations in AMPA and NMDA receptor levels can be a protective mechanism to counteract METH-induced neurotoxicity, but may also explain, at least in part, memory impairment presented by these animals (Simões et al., 2007). Studies using hippocampal cultures also demonstrated that the inhibition of Ca^{2+} release from endoplasmic reticulum prevented METH-induced cell death due to a decrease of NMDA receptor activation (Smith et al., 2010). These findings were attested by demonstrating the protective role of NMDA or AMPA receptor antagonists against METH-induced cortical DAergic system injuries (Gross and Marshall, 2009). Also, our group observed that a toxic METH concentration increased glutamate release in dentate gyrus-derived neurosphere cultures, and inhibition of NMDA receptors completely prevented METH-induced cell death (Baptista

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