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Review article

Amphetamine-related drugs neurotoxicity in humans and in experimental animals: Main mechanisms

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ABSTRACT

Amphetamine-related drugs, such as 3,4-methylenedioxymethamphetamine (MDMA) and methamphetamine (METH), are popular recreational psychostimulants. Several preclinical studies have demonstrated that, besides having the potential for abuse, amphetamine-related drugs may also elicit neurotoxic and neuroinflammatory effects. The neurotoxic potentials of MDMA and METH to dopaminergic and serotonergic neurons have been clearly demonstrated in both rodents and non-human primates. This review summarizes the species-specific cellular and molecular mechanisms involved in MDMA and METH-mediated neurotoxic and neuroinflammatory effects, along with the most important behavioral changes elicited by these substances in experimental animals and humans. Emphasis is placed on the neuropsychological and neurological consequences associated with the neuronal damage. Moreover, we point out the gap in our knowledge and the need for developing appropriate therapeutic strategies to manage the neurological problems associated with amphetamine-related drug abuse.

Abbreviations: AC, adenylyl cyclase; AcbSh, nucleus accumbens shell; AcbC, nucleus accumbens core; cAMP, cyclic adenosine monophosphate; CNS, central nervous system; CPu, caudate putamen; CREB, cAMP responsive element binding protein; CSF, cerebrospinal fluid; CYP, cytochrome P450 enzymes; DA, dopamine; DAT, DA transporter; 5,7-DHT, 5,7-dihydroxytryptamine; L-DOPA, 3,4-dihydroxy-L-phenylalanine; DOPAC, 3,4-dihydroxyphenylacetic acid; DPCPX, dipropylcyclopentylxanthine, adenosine A1 receptor antagonist; ERK, extracellular-signal-regulated kinase; FDA, Food and Drug Administration; fMRI, functional magnetic resonance imaging; GBR12909, vanoxerine, antagonist of DAT; GFAP, glial fibrillary acidic protein; GLU, glutamate; GSH, glutathione; HHMA, 3,4-dihydroxymethamphetamine; 5-HIAA, 5-hydroxyindoleacetic acid; HPA, hypothalamus–pituitary–adrenal axis; 5-HT, serotonin; HVA, homovanillic acid; HPLC, high-performance liquid chromatography; JAK, Janus kinase; JNK, c-Jun N-terminal kinases; ICV, intracerebroventricular; IL, interleukin; Mac-1, macrophage-1 antigen; MAO-B, monoamine oxidase type B; MAPK, mitogen-activated protein kinase; α-MeDA, α-methyldopamine; MDA, 3,4-methylenedioxyamphetamine; MDMA, 3,4-methylenedioxymethamphetamine; METH, methamphetamine; MK-801, dizocilpine, NMDA receptor antagonist; MOR-1, μ opioid receptor; a-MPT, alpha-methyl-para-tyrosine; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; MRI, magnetic resonance imaging; NA, noradrenaline; NAC, N-acetylcysteine; NET, NA transporter; 7-NI, 7-nitroindazole; NMDA, N-methyl-D-aspartate; NO, nitric oxide; 3-NT, 3-nitrotyrosine; nNOS, neuronal NO synthase; 6-OHDA, 6-hydroxydopamine; PD, Parkinson's disease; PET, positron emission tomography; PKC, protein kinase C; ROS, reactive oxygen species; RNS, reactive nitrogen species; SCH23390, dopamine D_1 receptor antagonist; SERT, 5-HT transporter; SN, substantia nigra; SNc, SN pars compacta; SOD, superoxide dismutase; SPECT, single photon emission computed tomography; TH, tyrosine hydroxylase; TNF, tumor necrosis factor; VMAT2, vesicular monoamine transporter; VTA, ventral tegmental area.

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Contents

1. Dopamine neurotransmission and neuroinflammation

The primary brain targets for the damage induced by both 3,4-methylenedioxymethamphetamine (MDMA) and methamphetamine (METH) are the striatum and the substantia nigra (SN). Thus, dysregulation of nigro-striatal dopaminergic system is the major cause of motor impairments induced by these drugs of abuse. Moreover, inflammatory effects of MDMA and METH play a significant role in the eventual dopaminergic dysregulation and symptom manifestation by these drugs. Hence, we will present a short overview on dopamine (DA) transmission and receptors and the role of neuroinflammation in neurodegenerative diseases with particular focus on these two drugs.

MDMA and METH may act as indirect DA agonists, producing their effects through DA receptors. These receptors are coupled to heterotrimeric G proteins and are classified into two families: D_1-like (which includes D_1 and D_5 receptors in mammals) and D_2-like (which includes D_2, D_3 and D_4 receptors) receptor families. Initially, these two families were defined functionally based on their ability to modulate adenylyl cyclase (AC) activity and cAMP accumulation in cells, but later this classification was confirmed by molecular cloning (Beaulieu and Gainetdinov, 2011). The D_1-like receptors are found exclusively post-synaptically and activate the $G_{as/olf}$ family of G proteins to stimulate AC and cAMP production. The D_2-like family are expressed both pre- and post-synaptically and activate the $G_{ai/olf}$ family of G proteins to inhibit AC and cAMP production (Beaulieu and Gainetdinov, 2011). There exist two variants of D_2 receptors: D_2-short (D_2-S) and D_2-long (D_2-L) (Giros et al., 1989; Monsma et al., 1989). The D_2-S variant is expressed mostly pre-synaptically and is involved in autoreceptor functions (*e.g.* control of DA release and regulation of extrasynaptic DA levels), whereas D_2-L is mainly a postsynaptic isoform (Usiello et al., 2000; De Mei et al., 2009). In addition, D_2-S potentiates DA transporter (DAT) activity *via* the formation of heteromeric protein–protein complexes with DAT localized in the dopaminergic terminals (Hadlock et al., 2010). Interestingly, the distribution of DA receptors is similar in humans and rodents (Ares-Santos et al., 2013).

The significance of DA receptors is reflected in the diverse action of DA in behavior and cognition, voluntary movement, motivation, punishment and reward, attention, learning and working memory (Granado et al., 2008a; Martín et al., 2008; Darmopil et al., 2009; Darvas and Palmiter, 2009, 2010; Ortiz et al., 2010; Murer and Moratalla, 2011; Espadas et al., 2012; Ruiz-DeDiego et al., 2015a,b). Moreover, DA receptors (*e.g.* D_1-like receptors) may mediate the interactions between glutamatergic and dopaminergic systems (Rodrigues et al., 2007). Consistent with this broad spectrum of activities, there is a wide expression of DA receptors in the brain. Both D_1-like and D_2-like receptor subtypes are present in all of the known DA projection fields in the CNS and their expression generally overlaps in most brain areas. Moreover, D_1-like and D_2-like receptors are highly expressed in the striatum, nucleus accumbens, olfactory bulb, amygdala, frontal cortex and SN and, at lower levels, in the hippocampus and ventral tegmental area (VTA) (Moratalla et al., 1996a; Beaulieu and Gainetdinov, 2011; Gangarossa et al., 2012). The striatum, one of the areas most affected by MDMA and METH, is the site with the highest concentration of DA in the brain. Although multiple DA receptor subtypes are present in the striatum, the D_1-like and D_2-like receptors are the most abundant in this area. Interestingly, D_1- and D_2-containing projection neurons are segregated in the striatum, as well as in the nucleus accumbens (Callier et al., 2003; Beaulieu and Gainetdinov, 2011; Suárez et al., 2014). D_1 receptor is selectively expressed in striatal projection neurons that form