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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 from 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.

Contents

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).

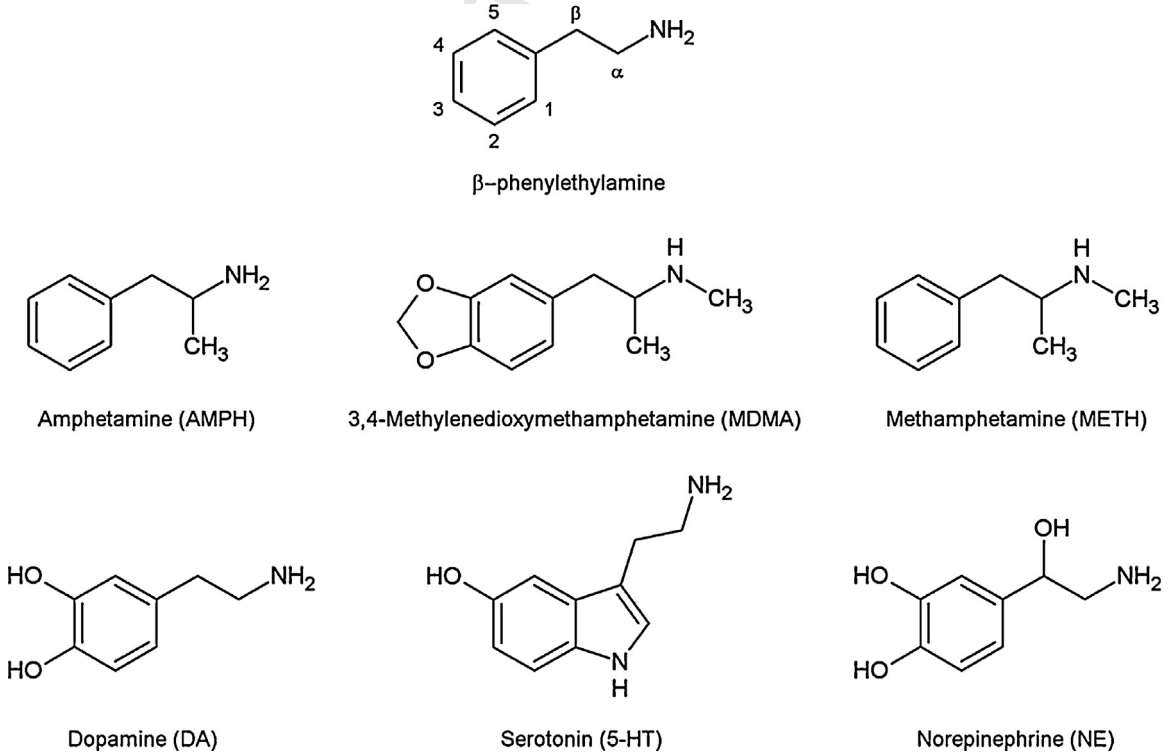

Fig. 1. Chemical structures of β-phenylethylamine (numbered), amphetamine (AMPH), 3,4-methylenedioxymethamphetamine (MDMA or "Ecstasy"), and methamphetamine (Meth, "Ice"). Amphetamines are structurally related to the monoamine neurotransmitters dopamine (DA), serotonin (5-HT), and norepinephrine (NE).

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