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Invited review

Designer psychostimulants: Pharmacology and differences

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ABSTRACT

More than 200 novel psychoactive drugs have been reported in Europe, with 73 added in 2012 and additional compounds encountered every week in 2013. Many of these are "designer psychostimulants" which aim to mimic the subjective effects of amphetamines, cocaine or 3,4-methylenedioxymethylamphetamine (MDMA; "Ecstasy"). Several drugs are based on the *beta*-ketoamphetamine cathinone chemical structure, others include aminoindanes, aminotetralins, piperazines, amphetamine analogues and pipradrol derivatives. Although a detailed analysis of the pharmacology of these novel drugs is largely lacking, a number of scientific studies have been reported in 2011–2013 and these are reviewed. All of the novel psychostimulants activate monoamine systems in the brain – with differing dopamine (DA) v serotonin (5-HT) preferences. Those activating principally DA systems are amphetamine-like stimulants, such as naphyrone, desoxypipradrol, 3,4-methylenedioxypyrovalerone (MDPV), and benzylpiperazine while those preferentially activating 5-HT mechanisms are MDMA-like or cocaine-like stimulants, such as mephedrone, methylone and other substituted cathinones, aminoindanes, aminotetralins and piperazines. The ability of mephedrone and other novel psychostimulants to substitute for methylamphetamine or cocaine in drug discrimination tests in rats, and the ability of mephedrone to induce conditioned place preference and to sustain self-administration behaviour suggests that this and other cocaine/methylamphetamine-like drugs have dependence liability.

This article is part of a Special Issue entitled 'CNS Stimulants'.

1. Introduction

Designer drugs are not a new phenomenon, the chemist Alexander Shulgin and his wife Ann described 179 phenylethylamine derivatives which they had synthesised and tested (Shulgin and Shulgin, 1991). These included a variety of stimulants, hallucinogens, and empathogens. Key substances which they described were 3,4-methylenedioxymethylamphetamine (MDMA, "Ecstasy"), and the related 3,4-methylenedioxyamphetamine (MDA), which were among the first "designer drugs" to become widely used – despite being illegal Class A substances in the UK (Iversen, 2006). Virtually all of the compounds described by the Shulgins either already were, or were subsequently declared illegal substances in the UK, but chemists soon found ways of designing other psychoactive phenylethylamines that could be marketed legally. The first of these new drugs to make a big impact was mephedrone (4-methylmethcathinone), which became prominent in the UK in 2008, 2009 and was declared illegal in 2010. Mephedrone was initially of high chemical purity and was seen as a legal alternative to MDMA. It was followed by a flood of other designer psychostimulants in recent years, many sold legally as "research chemicals" by internet websites (Power, 2013). The European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) have described the occurrence of more than 200 novel psychoactive substances in Europe, with 73 seen for the first time in 2012 and new compounds added every week in 2013 (Griffiths et al., 2013; EMCDDA, 2013). Although relatively little is known of the pharmacology of most of these novel chemicals, substantial scientific data have been reported on mephedrone and are beginning to emerge for other drugs in this class. For a comprehensive review see Dargan and Wood (2013).

2. Chemistry

Many of the novel drugs are *beta*-ketoamphetamines, based on the structure of cathinone, a naturally occurring substance found in the shrub khat (Fig. 1). Of the numerous cathinone derivatives, mephedrone, methylone (3,4-methylenedioxy-*N*-methylcathinone

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Nomenclature

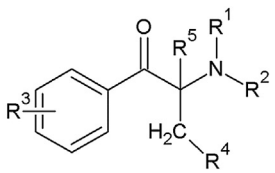
5-APB 5-(2-aminopropyl)benzofuran ('benzofury')
6-APB 6-(2-aminopropyl)benzofuran ('benzofury')
Benzedrone 1-(4-methylphenyl)-2-(benzylamino)propan-1-one
Butylone 1-(1,3-benzodioxol-5-yl)-2-(methylamino)butan-1-one
BZP *N*-benzylpiperazine
Cathinone *beta*-keto-amphetamine (2-amino-1-phenyl-1-propanone)
mCPP *meta*-chlorophenylpiperazine (1-(3-chlorophenyl) piperazine)
Desoxypipradrol 2-benzhydrylpiperidine (2-diphenylmethylpiperidine, 2-DPMP)
Ethylone 3,4-methylenedioxy-*N*-ethylcathinone
Fenfluramine 3-trifluoromethyl-*N*-ethylamphetamine
Flephedrone 4-fluoromethcathinone
5-IAI 5-iodo-2-aminoindane
MDAI 5,6-methylenedioxy-2-aminoindane
MDAT 6,7-methylenedioxy-2-aminotetralin
MDA 3,4-methylenedioxyamphetamine
MDMA 3,4-methylenedioxymethylamphetamine ("Ecstasy")
4-MEC 4-methyl-*N*-ethylcathinone
Mephedrone 4-methylmethcathinone (4-MMC)
Methcathinone 2-(methylamino)-1-phenyl-propan-1-one, (ephedrone)
Methylamphetamine *N*-methylamphetamine (*N*-methyl-1-phenylpropan-2-amine)
Methylone *beta*-keto-MDMA
MDPV 3,4-Methylenedioxypyrovalerone (1-(3,4-methylenedioxyphenyl)-2-pyrrolidino-1-pentanone)
Naphyrone 1-(naphthalen-2-yl)-2-(pyrrolidin-1-yl)pentan-1-one
1-Naphyrone 1-(naphthalen-1-yl)-2-(pyrrolidine-1-yl)pentan-1-one
PMA *para*-methoxyamphetamine
PMMA *para*-methoxy-*N*-methylamphetamine
TFMPP 1-(3-trifluoromethylphenyl)piperazine

or *beta*-keto-MDMA); and MDPV (3,4-methylenedioxypyrovalerone) have become widely used and these are the compounds for which the most detailed scientific data are available. Other chemical classes of designer psychostimulants are aminoindanes, aminotetralins, piperazines, benzofurans, pipradrols and amphetamine analogues (Fig. 2). A sophisticated chemical analysis of "legal high" products in the USA revealed numerous substances, and described the evolution of first and second generation products as new materials were marketed to avoid legal controls (Shanks et al., 2012).

3. Pharmacology

3.1. Neurochemical profiles of amphetamine, cocaine and MDMA (Ecstasy)

All of the novel psychoactive drugs mimic the existing psychostimulants cocaine, amphetamine and MDMA, although as with these existing agents there are subtle differences in their psychic effects. Amphetamine is the prototypical psychostimulant, causing agitation, insomnia, and loss of appetite – and, at higher doses, "amphetamine psychosis" characterised by paranoia, hallucinations and delusions. In experimental animals low doses of amphetamine cause hyperactivity and higher doses lead to stereotyped repetitive behaviours (Iversen, 2006). 3,4-Methylenedioxymethylamphetamine (MDMA; "Ecstasy") combines a psychostimulant effect with highly unusual changes in consciousness, leading to euphoria and an intense love of self and others, it is described as an "empathogen" (Iversen, 2006). MDMA illustrates the difficulty of drawing a clear distinction between "empathogens" and "psychostimulants" since it combines both properties. The subjective effects of cocaine, on the other hand, lie somewhere mid-way in the amphetamine/Ecstasy spectrum. All three classical drugs, and all of the newer "designer drugs" act by increasing extracellular levels of the monoamines dopamine (DA),



R^1	R^2	R^3	R^4	R^5	Name
H	H	H	H	H	Cathinone
Methyl	H	H	H	H	Methcathinone (ephedrone)
Methyl	H	4-Methyl	H	H	Mephedrone (4-MMC; M-CAT)
Ethyl	H	4-Methyl	H	H	4-Methylethcathinone (4-MEC)
Methyl	H	3,4-Methylenedioxy	H	H	Methylone (βk-MDMA)
Methyl	H	3,4-Methylenedioxy	Methyl	H	Butylone
Ethyl	H	3,4-Methylenedioxy	H	H	Ethylone (βk-MDEA)
Methyl	H	4-Methoxy	H	H	Methedrone (βk-PMMA)
Methyl	H	4-Fluoro	H	H	Flephedrone (4-FMC)
Benzyl	H	4-Methyl	H	H	Benzedrone
Pyrrolidinyl		3,4-Methylenedioxy	Ethyl	H	3,4-Methylenedioxypyrovalerone (MDPV)

Fig. 1. Some common cathinone derivatives.

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