Review

Drug Testing and Analysis

Received: 27 October 2010 Revised: 19 May 2011 Accepted: 19 May 2011 Published online in Wiley Online Library:

(www.drugtestinganalysis.com) DOI 10.1002/dta.313

Cathinone derivatives: A review of their chemistry, pharmacology and toxicology

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The purpose of this review is to evaluate what is currently known about the pharmacology of cathinone derivatives. Cathinone is the principal active constituent of khat responsible for the stimulant effects that have led khat to be known as a 'natural amphetamine'. Synthetic derivatives have been abused for their amphetamine-like stimulant effects, most notably methylone, methcathinone (ephedrone), and 4-methlymethcathinone (mephedrone). To date, cathinone and methcathinone have been studied most, demonstrating amphetamine-like effects in a range of *in vitro* and *in vivo* investigations, albeit less potently than amphetamines. In humans, cathinone derivatives are usually administered orally, and in some cases by insufflation. Methcathinone has a longer history of abuse, being produced from readily available starting materials, and administered by injection. Mephedrone has become the best publicised cathinone derivative, amid considerable media and public concern about its legal status, its ready availability, and reports of serious toxicity and deaths following its use. As a consequence, there has been a clampdown on cathinone derivatives, dramatically changing their legal status in a number of countries. However, little objective evidence-based comparative experiments have been conducted to date between these compounds and their related amphetamines in order to make clear risk judgements. Such assessments have largely been predictive in nature, based on their structural similarity to amphetamines. It can be assumed that, despite their illegal status, cathinone-related compounds will continue to be prevalent drugs of abuse for the foreseeable future.

Keywords: khat; cathinone derivatives; chemistry; pharmacology; toxicology

Introduction

Cathinone is the principal psychostimulant present in the leaves of the khat shrub (*Catha edulis*). Derivatives of cathinone have recently come to prominence as 'legal highs' and have been the subject of intense interest, resulting in restrictive legislation being introduced in a number of countries. The purpose of this review is to briefly examine the history of khat and the development of cathinone derivatives and their current global prevalence. The chemical similarities between cathinone derivatives and their relationship to amphetamine-like substances are also reviewed. Their pharmacokinetics, postulated neurochemical mechanisms, and pharmacological and toxicological effects are examined, along with any therapeutic indications for cathinone-related substances. Finally, the current legal status of the cathinone derivatives is discussed. This review focuses on the cathinone derivatives, with mention of khat where appropriate from a comparative perspective. More extensive reviews of the pharmacology of khat itself have recently been published.[1–3]

Historical overview

The major events in the history of khat and cathinone derivatives are summarized in Table 1. The khat shrub (*Catha edulis*) has a natural habitat which covers much of the Horn of Africa and the Arabian Peninsula.[4] Chewing the leaves of the khat plant and the resultant psychostimulant effects had been known within its area of cultivation for several hundred years.[5] The plant first became known to Europeans following its discovery and cataloguing by the Swedish botanist Peter Forsskål in the late eighteenth century. In the nineteenth century, advances in chemistry permitted the isolation of the active constituents of extracts from many remedies of plant origin, and attention focused on attempting to identify the active principle(s) of khat. This resulted in Fluckiger and Gerock identifying a 'katin' alkaloid in 1887. Further work in isolating and purifying this active principle was hampered by a number of obstacles. However finally, the substance cathine was isolated in 1930 and demonstrated to have the same chemical structure as d-norpseudoephedrine, the psychoactive alkaloid present in *Ephedra* species.[6] Just prior to the confirmation of the presence of cathine as a principle of khat, synthetic processes for two related compounds, namely for methcathinone (ephedrone) in 1928[7] and 4-methylmethcathinone (mephedrone) in 1929,[8] were established. The close structural relationship of these substances to amphetamine and its structural analogues led to an interest in developing these compounds for therapeutic purposes. Thus, methcathinone (ephedrone) was subsequently marketed as an antidepressant in the USSR during the 1930s and 1940s, and later developed by the US pharmaceutical company Parke Davis as a potential central nervous system (CNS) stimulant,[9] whilst amfepramone (diethylpropion) was first marketed as an appetite suppressant in the late 1950s.[10] During the middle part of the twentieth century, it became apparent that the psychostimulant properties associated with khat chewing could not be ascribed to cathine alone, as it was shown experimentally to have only modest stimulant properties.[11] An international initiative to further investigate possible contributors to the psychostimulant effects of khat culminated in 1975 with the

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Table 1. Significant dates associated with khat and cathinone derivatives

Time point	Observation
18th century	Swedish Botanist Peter Forskål catalogues the khat shrub
1887	Fluckiger and Gerock identify 'katin' alkaloid from a khat extract
1928	Synthesis of ephedrone (methcathinone) first reported
1929	Synthesis of mephedrone (methylmethcathinone) first reported
1930	Cathine (D-norpseudoephedrine) first isolated from khat
1930s	Methcathinone marketed as an antidepressant in the Soviet Union
1950s	Methcathinone investigated as a stimulant; amfepramone introduced as an appetite suppressant
1970s	Abuse of methcathinone in the Soviet Union
1975	Isolation of cathinone from fresh leaves of the khat plant
1985	Bupropion introduced as an antidepressant
1991	Methcathinone abuse appears in the USA
1994	Methcathinone scheduled
1996	Methylone patented as an antidepressant and antiparkinsonian agent
2000	Seizures of α-pyrrolidinophenone cathione derivatives
2004	Methylone begins to appear under the name 'Explosion'
2007	Appearance of mephedrone appears
2008	Appearance of flephedrone and naphyrone (NRG-1)
2009	Growing concerns about cathinone-derived 'legal highs'
2010	Legal restrictions enforced on cathinone derivatives in several countries

isolation of cathinone from the fresh leaves of khat.[12] Cathinone was shown to have much greater stimulant properties than cathine, but as cathinone degrades rapidly, this explained why it had not been identified previously when 'aged' leaves had been used for isolation purposes.[13] Moreover, there is evidence to suggest that cathinone can undergo quite complex structural rearrangements which can produce not only cathine, but also can form cyclic pyrazines or rearrangement to isocathinones (King, pers. comm). Clinical uses of other cathinone derivatives resulted in the introduction of bupropion as an antidepressant in the 1980s. Concerns about the abuse potential of cathinone derivatives were first highlighted with the widespread abuse of methcathinone ('Jeff') in the USSR from the 1970s and subsequently in the USA in the early 1990s.[14] This led, in 1994, to methcathinone being added to Schedule I of the UN Convention on Psychotropic Substances.[14]

Thus, by the early 1990s, the only cathinone-related substances that had been restricted were cathinone itself, cathine, and methcathinone. A growing number of cathinone derivatives were being evaluated for their therapeutic potential. For example, methylone, a cathinone derivative analogous to MDMA ('Ecstasy') was patented as an antidepressant and anti-Parkinsonian agent in 1996,[15] but no subsequent publications have resulted, nor has methylone being marketed for these conditions. Thus, through the 1990s, interest in cathinone-related compounds was restricted to isolated parts of the world, and to a limited number of cathinone-related substances. However, by the middle of the next decade, matters began to change with a number of cathinone derivatives appearing as 'legal highs', initially only in certain countries. For example, methylone emerged for sale under the trade name 'Explosion' around 2004 in Japan and the Netherlands;[16] it was one of the first products to be marketed via head shops and the Internet, which provided consumers with access to legal highs in a convenient manner. Certain α-pyrrolidinophenone derivatives had begun to appear in seizures in Germany in 2000, being a harbinger of a much more widespread phenomenon later in the decade.[17] Mephedrone (4-methylmethcathinone) became commonplace via these outlets in 2007 and 2008. It seems that mephedrone originally became available in Israel, but its production ceased in 2008 when the Israeli government banned it. This was followed by an unprecedented level of interest in mephedrone in certain parts of the world including Australia, Scandinavia, Ireland, and the UK. The next cathinone derivative to appear was flephedrone (4- fluoromethcathinone), and its related structural isomers 2- and 3-fluoromethcathinone.[18,19] The reasons for the increased interest in this range of cathinone derivatives (most particularly mephedrone) have been ascribed to the low cost, psychostimulant effects similar to illicit substances such as amphetamines and cocaine, and the decreasing purity of MDMA and cocaine,[20] as well as the ready accessibility of cathinone derivatives via head shops and the Internet, and of course their legal status.[21] At this time, tablets sold as Ecstasy were found to contain mephedrone.[20] The increasing interest in cathinone derivatives can be illustrated by the observation that, in 2008, of the 13 new psychoactive substances notified to the European early-warning system, six of these were cathinone derivatives.[22] A growing concern about the safety of mephedrone and its related derivatives has led to a range of restrictions in the countries where use has been prevalent, best exemplified by the UK government's decision in April 2010 to schedule cathinone derivatives as a collective group as Class B substances for which there is a penalty for possession and for dealing in such substances. Following the ban, products appeared purporting to contain naphthyl analogues of cathinone, typically labelled as NRG-1, NRG-2 or NRG-3, which were not covered by this original ban. Subsequently, in July 2010, the UK government placed these compounds in Class B of the Misuse of Drugs Act. By the end of 2010, mephedrone had been banned across all EMCDDA (European Monitoring Centre for Drugs and Drug Addiction) member states.[23]

Prevalence and level of interest in khat and cathinone derivatives

It is estimated that there are at least 10 million people globally who chew khat leaves on a daily basis,[24] with evidence of the spread of cultivation and use of khat to regions outside of the traditional area.[25] Khat use has spread over the last couple of decades to outside its traditional area of use as a consequence of the influx of immigrants of East African and Yemeni origin to the UK.[1] Due to the extensive air links from the areas of cultivation, supplies of fresh khat can reach these communities before any significant degradation of cathinone has occurred. As has been the case with

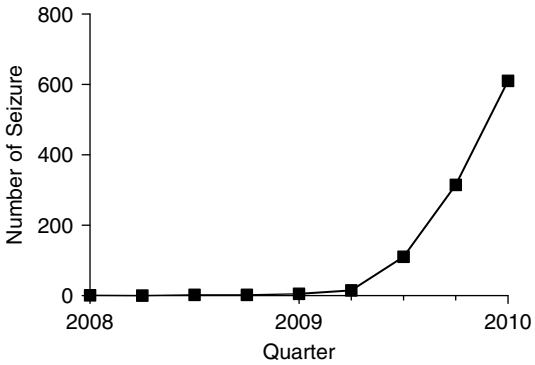

Figure 1. Seizure data for mephedrone in the UK, 2008–2010 based on figures released by the Forensic Science Service.[30].

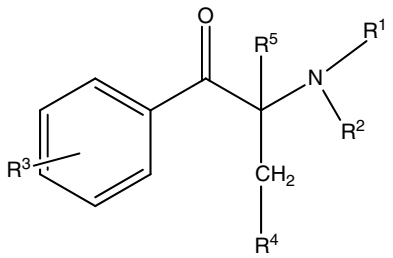

Figure 2. The generic structure for cathinone derivatives. In the case of cathinone, all of the R groups are H.

synthetic derivatives of cathinone, the Internet has also emerged as an important means of obtaining khat.[26]

The extent that mephedrone had become part of the club scene in the UK is illustrated by a survey conducted in 2009 in which over 40% of clubbers reported having used mephedrone, with nearly 34% reporting use within the previous month.[27] In this survey, mephedrone was ranked 4th amongst the drugs used within the last month, after cannabis, MDMA, and cocaine.[28] A recent survey of students in a district of Scotland conducted prior to the UK restrictive legislation revealed that 20% of respondents reported having used mephedrone at least once, with 4.4% of those using mephedrone reporting daily use.[29]

The recent growth in popular interest in cathinone derivatives can be seen by examining the Google 'Insights' search tool for the last five years. Although interest in khat and cathinone remained steady during this period, methylone interest started to grow from 2005 reaching a peak by 2009. Methcathinone first begins to appear in 2008, peaking in 2009, but with still considerable interest in 2010. Mephedrone also appears in 2008, but grows dramatically in 2009 and again in 2010. Peak interest in mephedrone was in the spring of 2010, when media attention was at its height. Flephedrone first appeared in 2009, and has shown a marked increase in interest in the first half of 2010. Thus, using this instrument, there has been an enormous level of interest in the cathinone derivatives. Another method of exploring the growth in cathinone derivatives is to assess the growth in its presence in seizures around Europe, which only began to appear in 2008. In the UK, the Forensic Science Service has released data for seizures of various substances, and the data for mephedrone are depicted graphically in Figure 1. These data clearly show a dramatic rise in seizures during 2009 and the early part of 2010, when the last records were available.[30] This rise has been accompanied by a similarly dramatic fall in the seizures for MDMA, perhaps related to reasons outlined earlier.

Chemical aspects

Structural relationships of the cathinone derivatives

The chemical structure of cathinone can be considered as the prototype, from which a range of derivatives have been developed. Figure 2 depicts the cathinone structure with the various points on the structure at which substituents are added to yield the wide range of cathinone derivatives. At present, there are approximately 30 known cathinone derivatives and their structural features are summarized in Table 2. All of these 'cathinones' can be considered as derivatives of phenethylamines with a β-keto group on the side chain.

Phenethylamines also include the amphetamines. This relationship has led to khat being described as a 'natural amphetamine', due to the stimulant properties of cathinone, and to a lesser extent, cathine. The only structural difference between cathinone and cathine is that cathinone possesses a ketone at the β-carbon whilst this is replaced by a hydroxyl group in the case of cathine. The naming of the cathinone derivatives can be complex and confusing with common, chemical, and slang names. For the purposes of this review, their most commonly encountered name will be employed.

Chemically, the cathinone derivatives can be thought to belong to a series of related clusters. First, *N*-alkylation at the R^1 and/or R^2 sites (either with methyl or ethyl groups) produces a series of alkylated cathinone derivatives. *N*-Methylation produces methcathinone, and a further methylation at position 4 on the ring produces mephedrone. *N*-Methylation at both R^1 and R^2 produces metamfepramone, whilst if these are ethyl groups the result is diethylpropion (amfepramone). Addition of a methyl group at position 4 on the ring of *N*-ethylcathinone yields 4-methyl-*N*-ethylcathinone. Methylation at R^1 and R^4 produces buphedrone. Methedrone has a methyl group at R^1 with a methoxy group at position 4 of the ring. Bupropion possesses a *N*-t-butyl group, and a chlorine at position 3 on the ring; modifications of the t-butyl group of bupropion are being investigated for therapeutic purposes.[34] A series of fluorinated cathinone derivatives consist of insertion of fluorine at various positions on the ring, the most common of which is 4-flouromethcathinone (flephedrone).[18] Ring substitution at R^3 with a methylenedioxy group produces a number of analogues of 3,4,-methylenedioxyamphetamines (MDAs). For example methylation at R^1 in this group produces methylone the β-keto derivative of MDMA, whilst elongation to an ethyl group at this site produces ethylone (bk-MDEA); methylation at the R^4 point produces pentylone. Close structural similarities exist between many of the cathinone derivatives, and the analyst needs to be also mindful of structural isomers, as exemplified by the determination by gas chromatography-mass spectrometry (GC-MS) and liquid chromatography-mass spectrometry (LC-MS) of bk-MDEA and bk-MBDB, and also their metabolites.[48]

A further number of cathinone derivatives possess a pyrrolidinyl moiety at the nitrogen atom of the cathinone structure. These pyrrolidine derivatives have as a prototype α-pyrrolidinopropiophenone (PPP) which has no substitutions at the R^3 to R^5 points. The most common substitution for this group is a 4-methyl insertion in the ring which results in MPPP (4-methyl-α-pyrrolidinopropiophenone). An insertion of an ethyl or a propyl

Table 2. Chemical structure of the cathinone derivatives

Substance	R^1	R^2	R^3	R^4	R^5	Reference
Cathinone	H	H	H	H	H	[31]
α-phthalimidopropiophenone	NR^2R^3 = phthalimide		H	H	H	[32]
Methcathinone (ephedrone)	Methyl	H	H	H	H	[33]
2-(methylamino)-1-(3-bromophenyl)propan-1-one (3-BMAP)	Methyl	H	3-Br	H	H	[34]
2-(methylamino)-1-(4-bromophenyl)propan-1-one (4-BMAP)	Methyl	H	4-Br	H	H	[34]
N,*N*-Dimethylcathinone (metamfepramone)	Methyl	Methyl	H	H	H	[31]
N-Ethylcathinone (ethcathinone, EC)	Ethyl	H	H	H	H	[32]
2-methylamino-1-phenylbutan-1-one (buphedrone)	Methyl	H	H	Methyl	H	No published data
4-Methyl-*N*-ethylcathinone	Ethyl	H	4-Methyl	H	H	[19]
4-Methylmethcathinone (mephedrone; 4-MMC; M-CAT)	Methyl	H	4-Methyl	H	H	[35]
Diethylproprion (Diethlycathinone; amfepramone)	Ethyl	Ethyl	H	H	H	[31]
1-(3-chlorophenyl)-2-[(1,1-dimethylethyl)amino)-1-propanone (Bupropion)	t-Butyl	H	3-Cl	H	H	[36]
2-(*iso*-propylamino)-1-phenylpropan-1-one (*i*-PAP)	Isopropyl	H	H	H	H	[34]
2-(*tert*-butylamino)-1-phenylpropan-1-one (*t*-BAP)	t-Butyl	H	H	H	H	[34]
3,4-Methylenedioxymethcathinone (Methylone; bk-MDMA)	Methyl	H	3,4-Methylenedioxy	H	H	[37]
3,4-Methylenedioxyethcathinone (Ethylone; bk-MDEA)	Ethyl	H	3,4-Methylenedioxy	H	H	[38]
β-keto-*N*-methyl-3,4-benzodioxyolylbutanamine	Methyl	H	3,4-Methylenedioxy	Methyl	H	[38]
(Butylone; bk-MDBD) Pentylone (bk-MBDP)	Ethyl	H	3,4-Methylenedioxy	Methyl	H	[39]
4-Methoxymethcathinone (Methedrone; bk-PMMA)	Methyl	H	4-Methoxy	H	H	[40]
4-Fluoromethcathione (Flephedrone, 4-FMC)	Methyl	H	4-F	H	H	[18]
3-Fluoromethcathinone (3-FMC)	Methyl	H	3-F	H	H	[18]
2-Fluoromethcathinone (2-FMC)	Methyl	H	2-F	H	H	[18]
α-Pyrrolidinopropiophenone (α-PPP)		Pyrrolidinyl	H	H	H	[41]
4-Methyl-α-Pyrrolidinopropiophenone (MPPP)		Pyrrolidinyl	4-Methyl	H	H	[42]
4-Methoxy-α-Pyrrolidinopropiophenone (MOPPP)		Pyrrolidinyl	4-Methoxy	H	H	[43]
4-Methyl-α-Pyrrolidinohexiophenone (MPHP)		Pyrrolidinyl	4-Methyl	Propyl	H	No published data
1-(4-methylphenyl)-2-(1-pyrrolidinyl)pentan-1-one (Pyrovalerone)		Pyrrolidinyl	4-Methyl	Ethyl	H	[44]
α-Pyrrolidinobutiophenone (α-PBP)		Pyrrolidinyl	H	Methyl	H	No published data
α-Pyrrolidinovalerophenone (α-PVP)		Pyrrolidinyl	H	Ethyl	H	[45]
4-Methyl-α-Pyrrolidinobutiophenone (MPBP)		Pyrrolidinyl	4-Methyl	Methyl	H	[46]
4-Methyl-α-Pyrrolidino-α-methylpropiophenone		Pyrrolidinyl	4-Methyl	H	Methyl	[46]
3,4-Methylenedioxy-α-pyrrolidinopropiophenone (MDPPP)		Pyrrolidinyl	3,4-Methylenedioxy	H	H	[37]
3,4-Methylenedioxypyrovalerone (MDPV)		Pyrrolidinyl	3,4-Methylenedioxy	Ethyl	H	[46]
3,4-Methylenedioxy-α-pyrrolidinobutyrophenone (MDPBP)		Pyrrolidinyl	3,4-Methylenedioxy	Methyl	H	[47]
1-napthalen-2-yl-2-pyrrolidin-1-yl-pentaon-1-one (β-naphyrone)		Pyrrolidinyl	benzyl	Ethyl	H	[39]

The substitutions relate to the generic cathinone structure of Figure 1.

group at the R^4 position results in pyrovalerone and MPHP (4-methyl-α-pyrrolidinohexiophenone) respectively. Replacement of the 4-methyl group of MPPP with a 4-methoxy group yields MOPP (4-methoxy-α-pyrrolidinopropiophenone). Again, there are the possibilities of isomers being produced, for example in the case of MPBP (4-methyl-α-pyrrolidinobutiophenone) and 4-methyl-α-pyrrolidino-α-methylpropiophenone which differ only by whether a methyl group is present at R^4 or R^5 points.[17] Finally there are 3,4-methylenedioxy derivatives, namely MDPPP (3,4-methylenedioxy-α-pyrrolidinopropiophenone) to which a methyl substitution at position R^4 produces MDPBP (3,4-methylenedioxy-α-pyrrolidinobutyrophenone[47]), or an ethyl substitution yields MDPV (3,4-methylenedioxypyrovalerone[46]).

The cathinone derivatives often have an amphetamine analogue. As can be seen from Figure 3, cathinone, ephedrone, and methylone are structurally analogous to amphetamine, methamphetamine and MDMA respectively, with the only difference being the β-keto moiety.[49] There is no common amphetamine analogue

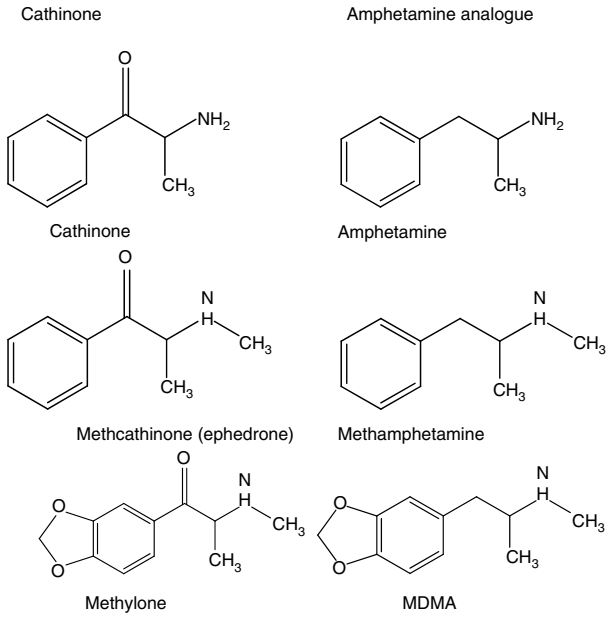

Figure 3. Chemical structures of some cathinone derivatives and their relationship to amphetamines.

of mephedrone. In a similar fashion to amphetamines, cathinone exists in two enantiomeric forms, with the pharmacological effects largely residing with the S-(−)-enantiomer, and this could well be the case for other cathinone derivatives, particularly methcathinone.

Preparations of khat and synthesis of cathinone derivatives

Khat leaves need to be consumed soon after harvesting, due to the rapid degradation of cathinone through the formation of a pyrazine dimer (King, pers. comm.). Thus, fresh khat leaves are the most sought-after form. The cathinone content can vary depending on the area in which khat is grown.[50] There is a dried form of khat leaves known as 'graba' that retains a relatively high content of cathinone, which means that the shelf life of the product can be extended.[51] For a short time, cathinone in powder form prepared in capsules was legally available in Israel (marketed as 'Hagigat') until this product was banned by the Israeli government in 2008.[52]

The most common route for the synthesis of mephedrone is using a 4-methylpropiophenone starting material, and then producing mephedrone using methylamine hydrochloride and dichloromethane.[32] Methcathinone can be synthesized in a clandestine fashion by the reaction of some readily obtainable raw materials, typically pseudoephedrine, potassium permanganate (used as an oxidising agent), and sulfuric acid.[33,53] In contrast, reduction of pseudoephedrine produces methamphetamine.[54] To date, this practice of methcathinone synthesis has been largely confined to the former USSR and Eastern Bloc countries. In the case of mephedrone, it has been reported that some users obtain this drug by home manufacture.[30] Mephedrone is most commonly encountered in powdered form, mostly at the time of writing originating from producers in Asia.[55] Mephedrone has been marketed as 'bath salts' or 'plant food' and include a warning 'not intended for human consumption'. Most of the other cathinone derivatives are usually marketed as powders or within capsules,

Naphyrone has been found in seizures of NRG-1 capsules and a recent analysis has revealed two isomers, namely α-naphyrone (1-napthalen-2-yl-2-pyrrolidin-1-yl-pentaon-1-one, naphthylpyrovalerone, O-2482) but also the newly identified β-naphyrone (1-napthalen-1-yl-2-pyrrolidin-1-yl-pentaon-1-one) which further complicates the picture from the perspective of correct identification of these derivatives.[47]

Purity of cathinone products

Recently, chemical analysis for the presence of cathinones has been undertaken in samples obtained via legitimate channels (i.e. via head shops and the Internet, when it was legal to do so), or as a result of seizures. Such samples have often demonstrated high purity for a single cathinone substance,[30,49] as can be judged by the analytical methods used and the standards employed, but not necessarily for the specific cathinone derivative on the label. This has been borne out by an investigation of products purported to be mephedrone or similar,[56] in which all samples tested did contain cathinone derivatives, but only 28% were for mephedrone, whilst the remaining samples had other cathinone derivatives present (such as flephedrone, methylone, butylone, and MDPV); local anaesthetics (lidocaine, benzocaine) were the most common non-cathinone substances present, presumably to minimize the discomfort reported when cathinones are administered by insufflation. Examining the same marketed products over a six-month period revealed that the cathinone constituents varied considerably.[57] Analysis of the composition of four capsules in Australia revealed that one contained 4-methylmethcathinone, a second α–phthalimidopropiophenone and 2-fluoromethamphetamine, whilst the final two capsules contained 4-methylcathinone, *N*-ethylcathinone, and α–phthalimidopropiophenone,[32] thus suggesting not only a mismatch between the label and the actual constituents, but the presence of more than one cathinone (as well as other pharmacologically active substances).

The pyrrolidino derivative MDPV was first identified in a seizure in Germany in 2007 and found to be of a high purity.[46] Despite generic bans of cathinone analogues that possess certain structural features, there are attempts to circumvent this by modifying the chemical structure sufficiently to be legally sold.[32] Thus, following the original ban in the UK in April 2010, there was a temporary loophole presented for the naphthyl analogues, marketed as NRG-1 and NRG-2 which began to be marketed as a 'legal alternative' to mephedrone and other banned cathinone derivatives. This loophole was closed in July 2010, when these substances were added to the scheduled list (Class B). Analysis of the composition of products purporting to be NRG-1 revealed that most did not contain naphthyl analogues, but other recently banned cathinone derivatives, in particular mephedrone, but also butylone, 4-methyl-*N*-ethylcathinone, flephedrone and MDPV either alone or in mixtures, whilst only a single sample (out of 13 tested) contained naphyrone; in some cases no stimulant compound other than caffeine was identified.[19] More recent analyses of NRG-1 and NRG-3 samples have revealed a range of pyrrolidino derivatives including MDPBP, MDPV and MPPP, as well as flephedrone and pentylone.[39] As mentioned previously, correct identification of cathinone derivatives has been hampered because of their close resemblance to each other, and the continual emergence of novel cathinones will make this a considerable analytical challenge in the future. Moreover, there is the possibility that cathinones may go through a process of cyclization and rearrangement to an

Table 3. Dose, route of administration for khat, and cathinone derivatives

Drug	Typical dose	Route of administration	Reference
Khat	100–500 g	Oral	[1]
Mephedrone	150–250 mg	Oral	[35]
	5–75 mg	Insufflation	[35]
Methylone	100–250 mg	Oral	[58]
Cathinone	200 mg	Oral	[52]
Methcathinone	60–250 mg	Intravenous	
		Oral, insufflation	[59]

isocathinone. This has been demonstrated for cathinone itself and may be the reason behind the presence of isocathinones in seizures (King, pers. comm.). The presence of such isomers is being increasingly acknowledged in regard to the pyrrolidino derivatives which can have more than one isomer.[47]

Pharmacokinetics of khat and cathinone derivatives

Due to the presence of the β-keto moiety, cathinone derivatives are much less lipophilic than amphetamines, and thus typically require much higher doses in order to produce equivalent effects to the amphetamines.[4] The doses and principal routes of administration of khat and the cathinone derivatives are depicted in Table 3.

The most common route of administration for khat is to chew the leaves and shoots of the plant, although infusions can be prepared. Continual chewing of the khat leaves results in the release of the psychoactive alkaloids cathinone and cathine.[60] The low concentration of these alkaloids within the plant means that, compared to other stimulants, large volumes of leaves need to be chewed in order to deliver a stimulant effect. Thus, chewing sessions typically last several hours, during which time between 100 and 500g of khat leaves are chewed.[1] Absorption occurs from two sites, namely the buccal cavity where the majority of the alkaloids are absorbed and also at the level of the small intestine which occurs after the juice is swallowed.[61] It is estimated that a typical chewing session of khat results in the absorption of the equivalent of approximately 5 mg of amphetamine.[62] Moreover, it has been estimated that chewing 100g of khat results in a delivered cathinone dose of 0.5 mg kg^{-1}.[63]

In the case of mephedrone, surveys suggest that 60–70% of mephedrone users report using nasal insufflation (snorting), or alternatively the oral route involving either swallowing a powder wrapped in paper ('bombing') or mixing in a drink. The oral route is often used to offset the nose burns associated with the insufflation route. Oral ingestion has been recorded in 60% of cases reporting mephedrone use to the UK National Poisons Centre, with insufflation being the route used in most of the other cases.[64] The doses of mephedrone administered vary between 15 to 250 mg for oral ingestion and 5 to 125 mg for insufflation. Repeated administrations ('stacking') take place in which 0.5–1g of mephedrone can be consumed during a continuous session, at the rate of 100–200 mg every hour.[65] Mephedrone is often taken in conjunction with other drugs, such as alcohol and cannabis, the purpose being either to enhance the mephedrone-induced effects, or to counteract the come-down effects which are similar to amphetamine or MDMA, and consist of fatigue, dysphoria, aches, and pains, and amnesia.[65] Methylone is typically administered at a dose of 100–250 mg. There is limited information on the doses employed for the other cathinone derivatives.

The plasma concentrations of cathinone and cathine reach their peak within approx. 2–2.5 h after beginning to chew khat,[66,67] whilst ingestion of capsules of cathinone have shown a quicker peak level of 1.5 h.[63] When taken by insufflation, mephedrone's effects start within 10–20 minutes and last 1–2 h; with the oral route the effects take longer to peak (i.e. 20–40 min), lasting 2–4 h.[65]

Following absorption, all cathinone derivatives have been shown to undergo extensive Phase 1 metabolism (Figure 4). For example, cathinone is metabolized to norephedrine and norpseudoephedrine/cathine[63,66,68,69] involving the Phase 1 reduction of the β-keto moiety to an alcohol.[68] The metabolism of cathinone has been shown to be stereoselective with the principal metabolite of S-(−)-cathinone being R,S-(−)-norephedrine, whilst R-(+)-cathinone is metabolized to R,R-(−)-norpseudoephedrine.[69] Methcathinone also undergoes reduction, which is then followed by N-demethylation of the methyl group.[70] Mephedrone is metabolized via N-demethylation and/or reduction of the β-keto to the corresponding alcohol.[71] The 3,4-methylenedioxy ring-substituted cathinones (e.g. methylone, butylone, and ethylone) are metabolized by demethylenation, and also by similar Phase 1 reactions to those of other cathinones, e.g. *N*-dealkylation, *O*-methylation and reduction of the β-keto moiety.[37,72] The metabolism of a number of pyrrolidino cathinone derivatives has been characterized.[42,43,73–75] The β-keto position of pyrrolidino derivatives is converted into the resultant alcohol in a similar way to other cathinones, and where a methyl group exists on the phenyl ring, this will be hydroxylated and oxidized to a carboxylic acid. The pyrrolidine ring undergoes a range of biotransformations including hydroxylation and dehydrogenation to a lactam. In addition the pyrrolidine ring can undergo transformation to a primary amine.[38] Fluorinated cathinone derivatives (such as flephedrone) can be presumed to be more resistant to metabolism due to the challenge of enzymatically breaking the C-F bond.[76]

The majority of the cathinone derivatives are eliminated as metabolites via the urine, either in a free form or conjugated via Phase 2 glucuronidation and/or sulfation reactions.[38] For example, when cathinone is administered orally, over 90% has undergone some form of metabolism prior to being excreted in the urine,[61,68] mostly as norephedrine and cathine.[67]

Neurochemical actions

In order to elucidate the neurochemical mechanism of action of cathinone derivatives, *in vitro* investigations are employed using cell and synaptosomal preparations in which the ability of the chemical substances to interfere with monoamine (i.e. dopamine, noradrenaline, and serotonin) reuptake and/or release can be investigated. Such investigations can reveal the relative potency of drugs for particular neurochemical targets and allow comparisons to be made between structurally similar compounds. Such sites have been the focus of attention as amphetamines have these sites as their principal target of action. As a consequence the effects of cathinones on these targets are often compared to amphetamines. Data on the affinity of cathinone derivatives for these sites is limited, but Table 4 summarizes the current literature.

Cathinone derivatives have displayed enhanced release of dopamine. For example, using synaptosomal preparations, it has

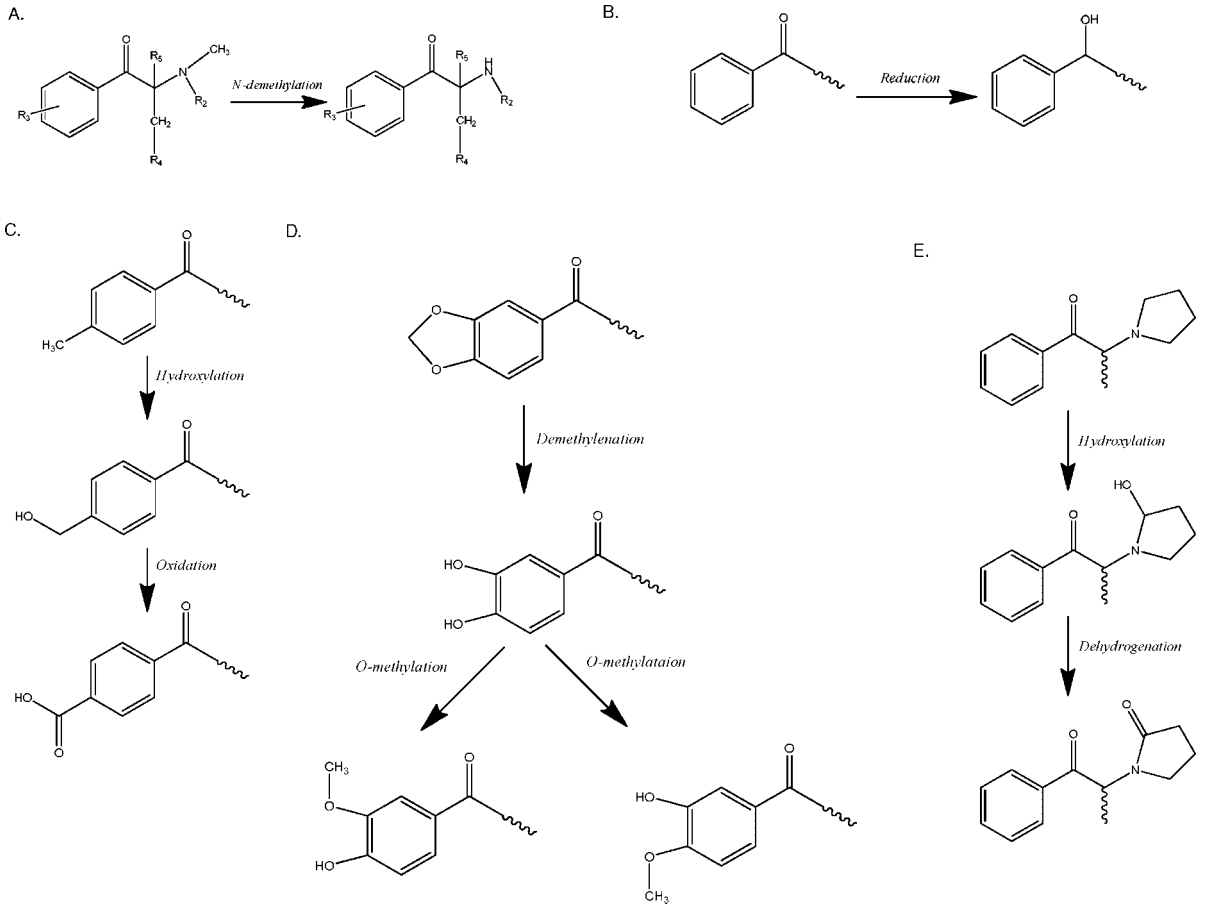

Figure 4. Metabolic pathways for cathinone derivatives. (A) depicts the removal of a methyl group that is often present at position R_1. (B) depicts the conversion of the βketone to an alcohol. (C) depicts the creation of a carboxylic acid from the methyl group on the phenyl ring. (D) depicts the breaking of the dioxymethylene structure, firstly by demethylenation, and then followed by O-methylation at one of the corresponding hydroxyl points. (E) Depicts the metabolism of the pyrrolidine into a lactam. [38].

Table 4. The effects of cathinone derivatives on *in vitro* inhibition of monoamine reuptake

Drug	Dopamine	Noradrenaline	Serotonin
Cathinone	+++	+++	++
Methcathinone	++++	++++	+
Methylone	+++	+++	++
Bupropion	++++	++++	+
Pyrovalerone	++++	+++	+
Amphetamine	+++	++++	+
Methamphetamine	++++	++++	++
Cocaine	++++	++++	++++
MDMA	++++	++++	++++

Results are expressed as relative inhibition using IC_{50} or K_i values.[77–81] Experiments involved either the use of rat synaptosomes or cells transfected with the appropriate human transporter. + = 0.3–1 μM; ++ = 1–3 μM; +++ = 3–10 μM; ++++ = 10–30 μM. MDMA = 3,4-methylenedioxymethamphetamine.

been demonstrated that cathinone[82,83] and methcathinone[84] can increase the release of dopamine from its stores. Moreover, methcathinone and methylone have demonstrated a similar potency of inhibition of the dopamine transporter in human platelets to methamphetamine and MDMA.[79] Similar findings have been found when methcathinone and cathinone have been compared to amphetamine and methamphetamine where they have demonstrated, if anything, a greater potency for provoking the release of dopamine and noradrenaline.[85] Methcathinone has been shown to dose-dependently increase extracellular dopamine levels in the rat.[84] The effects of cathinones on dopamine release can be attenuated by administration of dopamine receptor antagonists[86] or by prior administration of the dopaminergic neurotoxin 6-OHDA which will deplete dopamine from its stores.[87,88] Cathinone is a more potent inhibitor of monoamine oxidase (MAO) activity than amphetamine,[89] with a greater selectivity for MAO-B inhibition than MAO-A.[90] MAO-B is the principal isoenzyme responsible for the degradation of dopamine, and inhibition of this isoenzyme will contribute to enhancing the synaptic availability of dopamine. Chronic administration of cathinone[91] or methcathinone[84] to rats produces a depletion of the dopamine content in the brain similar to that observed following chronic administration of to amphetamine and cocaine.[92] Such dopamine depleting properties have also been demonstrated following chronic administration of an extract made from khat leaves.[93] Cathinone[94] and methcathinone[85] have been shown to provoke the release of noradrenaline at similar potency to amphetamines. Methcathinone and methylone have exhibited similar inhibition of noradrenaline reuptake to methamphetamine and MDMA.[79] There have been

conflicting findings in relation to the effect of cathinone on the serotonergic system. It has been found that cathinone can increase the release of serotonin from rat synaptosomal[82] and inhibit serotonin reuptake from human platelet[79] preparations, but with one-third of the potency of amphetamine. Other studies have shown a modest effect on serotonin release with cathinone and methcathinone, equivalent to amphetamine, but less potent than that seen with methamphetamine.[85] Chronic administration of cathinone has not been shown to reduce the concentration of serotonin in rat brain,[95,96] but did reduce the serotonin transporter activity, albeit to a far lesser extent than that following administration of amphetamines such as amphetamine and methamphetamine.[97]

Pharmacological effects

Effects in humans

Following khat consumption, a spectrum of pharmacological effects occur including central (increased alertness and vigilance, euphoria, increased sensory stimulation, hyperthermia, anorexia), as well as peripheral effects (increased respiration rate, heart rate, blood pressure) that have been well documented,[98–100] and which resemble those observed following amphetamine use. The appearance of psychiatric symptoms has been reported following khat chewing, ranging from psychoses of different kinds[5] to depression.[101,102] The psychotic symptoms that have been reported appear to resemble those seen with other psychostimulant drugs such as amphetamine and cocaine.[92,101] However, little controlled investigation has taken place in this area,[103,104] and in a similar fashion to heavy cannabis use, the excessive consumption of khat may unmask a predisposition that the subject might have for psychosis.[5,104] This may particularly be the case for immigrants who have had the additional upheaval of dislocation from their home country,[105–107] or post-traumatic stress disorder brought on as a consequence of civil war.[103,108] In Yemen, the incidence of psychiatric disorders has been demonstrated to be similar between those that chew khat and those that do not.[109] There have been suggestions that khat chewing may have a profound effect on the ability to drive and thus be responsible for a high proportion of traffic accidents in countries where its use is commonplace.[110] However, to date there has been little controlled examination of a causal link, which means that there is an over-reliance on anecdotal reports.[111]

The cathinones have a distinct cluster of pharmacological effects. For example, the effects of mephedrone can be thought of as having both psychostimulant (i.e. an amphetamine-like) and hallucinogenic MDMA-like properties. The MDMA-like hallucinogenic effects are distinct from those of classical hallucinogens such as LSD, probably due to differing 5-HT receptor activity profiles.[112] Many of the effects of mephedrone can be ascribed to a general sympathomimetic activation, with many of the effects on the central nervous system being similar to those observed with khat, but greatly enhanced due to the higher doses employed, for example, 'head rushes', followed by euphoria, boundless energy, talkativeness, and time distortions.[65] Similarly, methcathinone has demonstrated a range of central effects, including psychomotor agitation, tremors, and insomnia.[113] A survey of students who had reported taking mephedrone found that over half had experienced some form of adverse effects, mainly associated with the CNS nasal/respiratory and cardiovascular systems.[29]

Table 5. Doses of cathinone derivatives that induce locomotor activity in rodents

Drug	Dose range	Reference
Khat extract	200–1600 mg kg^{-1} po, rats	[118]
Cathinone	1–20 mg kg^{-1}, po, sc, ip, rats	[118]
Methcathinone	1–10 mg kg^{-1} ip, mice	[120]
Bupropion	10–15 mg kg^{-1} ip, rats	[34]
Methamphetamine	0.3–3 mg kg^{-1} sc, rats	[122]
Amphetamine	1.25–5 mg kg^{-1} sc, rats	[123]
MDMA	5–20 mg kg^{-1} ip, rats	[124]

Animals received single administrations of the test compounds and locomotor activity was assessed in a variety of ways, involving either novel arenas or home cage environments. MDMA = 3,4-methylenedioxymethamphetamine. po = oral; sc = subcutaneous; ip = intraperitoneal.

A major concern is to establish whether regular use of khat or cathinone derivatives have addictive potential. There does seem to be evidence to suggest that regular use of khat can produce compulsive behaviour in certain individuals,[106,107,114,115] and in some of the eastern African countries, 5–15% of the population have been estimated to have a dependence on khat.[102] There is evidence for a strong craving responses elicited in mephedrone users revealed as a strong compulsion to self-administer the drug on repeated occasions.[29,65] High proportions (over 80%) of users have reported a strong craving for mephedrone,[20] and users begun to appear in drug addiction treatment centres.[116]

Effects in laboratory animals

When the central brain activity of rats is examined using EEG patterns, administration of an extract of khat produces a biphasic dose response. Lower doses of the khat extract were examined that are equivalent to pharmacological doses of cathinone (50–100 mg kg^{-1}) and these produced EEG stimulation, whilst extracts that contained higher doses of cathinone (400 mg kg^{-1}) produced an initial stimulation followed by a profound depression of the EEG pattern.[117]

Administration of a khat extract and cathinone to rats produces a range of behavioural responses such as an increase in locomotor activity, stereotyped movement, and anorexia,[115] which can be expected when we consider the effects on the dopaminergic, and to a lesser extent serotonergic systems that have been observed *in vitro*. The most studied substance has been cathinone itself, which produces increases in locomotor activity in a number of experimental animal species,[1] producing locomotor effects in mice and rats.[117] In rodents, S(−) methcathinone was found to be much more potent at inducing locomotor activity than the R(+) enantiomer[118,119] and twice as potent as (+)amphetamine.[119] However, other studies have suggested in rats that both enantiomers of methcathinone are equipotent at producing locomotor activity.[120] The locomotor effects of methcathinone can be attenuated by substitution at position 4 of the phenyl ring to 4-BMAP (2-(methylamino)-1-(3-bromophenyl)propan-1-one); this insertion is site specific as the corresponding bromide substitution at position 3 (3-BMAP; 2-(methylamino)-1-(4-bromophenyl)propan-1-one) produces a qualitatively similar locomotor response to methcathinone.[33] A summary of the doses employed with cathinone derivatives that induce locomotor activity in rats is depicted in Table 5, alongside methamphetamine, amphetamine,

and MDMA. Although this is a measure of general activity, it is useful as a comparative *in vivo* measure to explore the dose range at which locomotor activity is elicited. It can be seen that all of the cathinone derivatives elicit an increase in locomotor activity, at a similar dose range.

In the rat forced-swim test, a predictive paradigm for detecting antidepressant activity, methcathinone (5 mg kg^{-1}) has displayed reductions in immobility time, as has bupropion (5 and 10 mg kg^{-1}), that were at least as pronounced as that observed with the marketed antidepressant desipramine (10 mg kg^{-1}), suggesting antidepressant potential for these compounds.[33] However, the evident locomotor stimulant effects described earlier has been a property which is not desirable with these compounds, and may at least in part explain their activity in this test. Interestingly, amphetamine administration produces a reduction in immobility time, but at doses that elicit high levels of locomotor activity, and is thus thought of as a false positive in this test.[124]

Another property that has been explored in animals is the ability of cathinones to produce behavioural sensitization, i.e. that upon repeated administration, the behavioural response to a substance becomes enhanced. This is a well-known phenomenon associated with repeated psychostimulant administration.[125] A sensitization to the locomotor and stereotypy effects of an extract of khat and cathinone have been observed following repeated administration in rats, which is of a similar magnitude to that seen with amphetamine,[127] which can be blocked by concurrent administration of the second-generation antipsychotic drug, clozapine.[93]

Drug discrimination studies are conducted to see whether an animal, once conditioned to receiving a certain drug, will evoke similar behavioural patterns upon substitution with another drug. Methcathinone will substitute for cocaine and amphetamine,[128,129] a property shared by bupropion,[130,131] whilst methylone will substitute for MDMA, but not for amphetamine.[31] These results suggest a close relationship between cathinone derivatives and their related amphetamines. In addition, baboons will self-administer methcathinone,[132] and rats and rhesus monkeys have been shown to self-administer cathinone[133,134] suggesting that it has some rewarding properties, which might not be surprising when one considers its amphetamine-like effects on the dopaminergic system. Administration of extracts of khat to rats has been shown to increase sexual behaviour at pharmacological doses, but higher doses will inhibit this behavior.[135] Cathinone itself has also exhibited increases in sexual behaviour when given repeatedly to rats.[136]

Toxicological effects

Acute toxicity

Khat itself has not been associated with many acute toxic effects following chewing, probably because, due to its bulk, it is very difficult to release sufficient amounts of cathinone and other substances to produce acute toxic effects. This is in contrast to the synthetic cathinone derivatives, which, being available as powders, can ensure that very high concentrations can be achieved in the bloodstream. However, implicating a specific cathinone in precipitating toxic effects can prove to be a challenge. For example, many of the reports to date have not appeared in peer-reviewed literature, or have often been retrospective surveys from poison control centres, or personal interviews with the consumers of these products. From the consumer perspective, the compounds that they have ingested may not match with the labelling of the products, and the forensic confirmation of cathinones has been hampered by a lack of analytical standards that would aid in their correct identification.

Most concern in the regard of acute toxicity has focused on mephedrone, with several deaths and toxicity being attributed by the media to its use. It is only relatively recently that published reports of the toxic consequences of mephedrone have begun to appear. The symptoms observed following high doses of mephedrone are exaggerations of its pharmacological effects, most particularly excessive CNS (seizures, agitation, paranoia, hallucinations) and cardiovascular (tachycardia, hypertension) stimulation,[137–139] which are somewhere between the toxic effects of amphetamine and MDMA. When admitted to hospital, most of these effects wear off of their own accord, with some subjects requiring benzodiazepines to counteract the excessive agitation and anxiety. The picture is complicated by the regular concomitant administration of other substances, particularly alcohol and other legal highs alongside mephedrone.[138] There have been a number of deaths where mephedrone has been considered to be involved, but few of which have been confirmed following forensic toxicological evaluation.[64] The first death where mephedrone was confirmed to be the causative agent was in 2008 in Sweden.[137] A published finding from the UK revealed that the death of a 46-year-old man was caused by a combination of mephedrone and heroin,[140] and others from Scotland have found a number of other compounds present, alongside mephedrone following toxicological screening.[141] However, the degree of concern regarding cathinone derivatives can be seen by the dramatic increase in calls to the UK National Poisons Information Service in relation to these substances beginning in the middle part of 2009.[63] There have been limited published studies with relation to the other cathinone derivatives. Methcathinone has been associated with toxicity and a number of fatalities in the USSR and symptoms are similar to those previously described for mephedrone.[33] Similarly, overdose with cathinone will produce exaggerated CNS and cardiovascular effects.[52]

Chronic toxicity

Khat chewing over a prolonged period has been reported to produce a number of adverse consequences, ranging from psychiatric disturbances to damage to the major organs of the body.[142] In addition, long-term khat chewing has been associated with neurological disorders.[143] The most documented long-term toxicological effects that have been found with cathinone derivatives probably related to Parkinson's-like symptoms seen following methcathinone administration, in intravenous abusers from the former USSR and Eastern bloc countries. These symptoms are not believed to be related to methcathinone itself, but rather due to manganese poisoning brought about by the high concentrations of manganese present in the clandestine preparations of methcathinone.[144–147] Such symptoms are refractory to a number of treatments including chelation therapy and l-DOPA.[148,149] An extensive review of this area concludes that manganese is probably the sole causative agent for the Parkinson's symptoms in these patents, with little contribution to the neurotoxicity being associated with dopamine depletion, which helps to explain the lack of success with implementation of l-DOPA therapy.[150] In the USA, a study examined the neurotoxic effects of methcathinone in which reductions in the number of dopamine transporters in the brain were observed with long-term

(but currently abstinent) methcathinone users which are similar to those seen with abstinent methamphetamine users,[59] suggesting that methcathinone administration can have some long-lasting effects on the dopaminergic system in humans, in situations where manganese contamination is not implicated.

In animals, repeated administration of either enantiomer of methcathinone has been shown to be neurotoxic to the central dopaminergic system in rats by reducing the number of dopamine transporter sites, whilst the S-enantiomer has also caused a reduction in serotonin transporter density.[121] Moreover, repeated administration of methcathinone has been shown to reduce central serotonin and dopamine content, as well as the activity of tryptophan hydroxylase and tyrosine hydroxylase, the enzymes responsible for the synthesis of serotonin and catecholamines, respectively.[151]

Therapeutic uses

A number of therapeutic uses have been claimed for khat. For example, khat has been used to treat a number of respiratory conditions including cough, as a traditional remedy. This has been confirmed experimentally with the observation that cathinone is able to relax airway smooth muscle in preparations stimulated by cholinergic agents.[152] Khat chewing is also associated with reducing the sensations of hunger;[153] cathine and norephedrine have been used for this purpose.[115] This has also been the basis of exploring cathinone derivatives for these properties, most particularly amfepramone (diethylpropion) which was introduced in the late 1950s as an appetite suppressant.[10] Khat has been long used for its ability to offset fatigue,[154] and this has been illustrated in clinically controlled experiments with pyrovalerone.[155] Khat has also been used as an aphrodisiac,[4,156,157] a property which was one of the main selling points of Hagigat, a preparation of cathinone.[52]

Antidepressant properties have also been claimed for khat and cathinone derivatives. For example, methcathinone was originally developed as an antidepressant in the USSR in the 1930s.[77] Although methylone was originally patented as an antidepressant, it has not been developed for this purpose. Naphyrone has been explored for its antidepressant properties,[80] whilst the related compound bupropion has a long history of use as an antidepressant, being first marketed in 1985 in the USA. Analogues of methcathinone and bupropion have been developed which have demonstrated antidepressant properties in the rat forced-swim test without any concomitant locomotor stimulant effects and have been described in a previous section.[34] However, no follow-up data have been found to indicate whether these compounds have been developed further for this purpose.

Bupropion has been marketed for a number of years under the trade name Zyban as an aid in the cessation of cigarette smoking,[36] as well as potentially in the treatment of cocaine and methamphetamine dependence.[81] Recently, a number of analogues of bupropion that possess a greater affinity for the dopamine transporter than for the noradrenaline transporter have been synthesized. The structural change that produced a more selective blockade of the dopamine transporter involved elongation of one of the carbon side chains emanating from the terminal nitrogen; compounds with this modification produced less cocaine-like properties in animal studies.[80] A similar strategy has produced bupropion analogues that have a greater propensity for inhibiting nicotine-evoked responses in mice.[158,159] Thus, structural adaptations to bupropion are being actively pursued in order to produce more effective treatments for nicotine, cocaine, and methamphetamine dependence.

Legal status

The status of khat has been a subject of considerable debate. Although the active alkaloids cathine and cathinone which are derived from khat have been listed for over 40 years, the legal status of khat is a grey area, as it is not scheduled within the UN conventions.[160] Some countries have banned khat use, but often this has proven to be extremely difficult in the countries in which khat cultivation and use are part of the fabric and culture of the society, as well as the potentially disastrous economic consequences.[3] As a consequence, such attempts to restrict its use have not proved to be successful.[1] In Europe, there is a patchwork of different viewpoints regarding the legality of khat.[161] For example, khat is illegal in many European countries including Ireland, France, Germany, and much of Scandinavia[161] whilst it is accepted within the Netherlands[108] and in the UK it is considered a vegetable[162] and thus lies outside of restrictive legislation at the current time. As the alkaloids from the khat leaves are of a low concentration, and thus requires chewing of large amounts of material over a prolonged time, it has been considered that the practice of khat chewing would not spread beyond the areas of cultivation or beyond the immigrant communities from such areas, and perhaps explains the attitudes in some countries (most notably the UK) to adopting a tolerance of this product, in contrast to the cathinone derivatives.

Cathinone derivatives have become the subject of intense legislation over the last couple of years. Prior to this cathinone and methcathinone (Schedule 1) and cathine (Schedule IV) had been listed by the United Nations 1971 Convention on Psychotropic Substances. A number of European countries have introduced controls on hitherto legal cathinone derivatives. These changes probably can be marked by individual cathinones being banned in certain countries. Mephedrone has provoked the most attention, being banned in Sweden in December 2008. Since this time, restrictive legislation has been introduced in Denmark, Germany, Estonia, Sweden, Norway, the Netherlands, Finland, and Ireland, making mephedrone illegal, often alongside a number of named cathinone derivatives. In April 2010, the UK Advisory Council on the Misuse of Drugs took the unprecedented step of recommending that a whole range of cathinone derivatives be controlled under this umbrella term as Class B drugs, i.e. the same class as the amphetamines.[28,77,163] This was followed in July 2010 with the ACMD recommending that naphyrone and associated compounds be added to the Class B list. Mephedrone is now banned in all EMCDDA member states.[23]

Conclusions

This review has explored the properties of khat and cathinone derivatives, and it can be seen that the use of these substances has provoked considerable interest and debate over the last few years. Khat chewing has been a cultural phenomenon of the Horn of Africa and Arabian Peninsula for centuries, and an awareness of this practice has only relatively recently became known to the global community. The culture of khat chewing is strongly embedded in the people of this area, a practice that they have

been able to take with them to far-flung parts of the world. The mild psychostimulant effects that result from khat chewing have meant that the United Nations has not deemed it necessary to control this plant, and thus restrictions on its availability have been largely left to individual countries which have resulted in suppressive legislation in some countries, whilst their neighbours have taken a much more tolerant approach. A pragmatic approach for the control of khat involving harm reduction and regulation innovations has been recently mooted as a way forward which attempts to find a middle ground between acknowledging the economic value of khat as a cash crop, tempered against concerns about its use.[24,164]

The identification of the active principles of khat has helped in being able to explain the stimulant actions of khat chewing. Cathine and cathinone are related to the naturally occurring ephedrine, as well as to the synthetic amphetamines, coining the term 'natural amphetamine' to explain the actions of khat. A number of derivatives of cathinone were synthesized and clinical applications begun to be proposed for them. The most prominent of these was methcathinone, originally marketed as an antidepressant, but which became a widely abused drug that was ultimately added to the UN list in the 1990s. A legal loophole meant that a range of synthetic legal highs began to be marketed, with a large representation of cathinone derivatives, with mephedrone being the most widely marketed. The last few years have witnessed attempts by many countries to close this legal loophole by banning these substances, either as individual named compounds, or under collective groupings. Such restrictive legislation has been introduced on the premise of the structural similarities of these cathinone derivatives to cathinone and methcathinone, and also to the amphetamines, as little objective experimental investigation of these substances has taken place. There has been considerable debate on the issue of restricting the cathinone derivatives, with little firm experimental data available from which to make evidence-based decisions.[165] Thus, there is a great need to be able to study these cathinone derivatives both at a fundamental level by comparing their potencies with amphetamines and other stimulant drugs, whilst also monitoring the incidence of adverse effects in those who have taken these compounds. The latter area of investigation naturally will prove to be extremely difficult in countries where admission of taking a cathinone derivative is an offence. However, such studies will be extremely important in estimating the risk of toxicological effects with cathinones and in devising plans for minimizing such risks in the future.

Acknowledgements

The author gratefully acknowledges the helpful and constructive comments and guidance provided by the editors and reviewers in the preparation of this review.

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