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Minireview

Synthetic cathinones: Chemical phylogeny, physiology, and neuropharmacology

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ABSTRACT

This mini-review summarizes the history of cathinone and its synthesized derivatives from early records to the present day, including the appearance of synthetic cathinones in the drug combination known as bath salts. Bath salts may consist of one compound (MDPV) or combinations of MDPV and one or more other synthetic cathinones, which may also appear alone without MDPV. We briefly review recent in vitro studies of bath salts components alone or in combination, focusing on pharmacological and biophysical studies. Finally we summarize new data from in vivo procedures that characterize the abuse-related neurochemical and behavioral effects of synthetic cathinones in rats.

Contents

Introduction

The following narrative traces some of the initial key developments and findings leading up to the class of agents now termed "*synthetic cathinones*". Cathinone is a naturally-occurring stimulant found in the khat plant. The "*synthetic cathinones*" are analogs of cathinone. According to Alles et al. (1961) the first written record of khat use was in the 14th century, and khat use continues to this day. The fresh leaves of the shrub *Catha edulis* are chewed or occasionally brewed as a tea in the Arabian Peninsula and in certain regions of Eastern Africa for their central stimulant effects. The leaves, or concoctions prepared there from, are known by a variety of names depending on specific geographic location (e.g. khat, k'at, kat, kath, gat, miraa, qat, Abyssinian

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tea, Arabian tea, Somali tea). Millions of people in these regions use khat regularly.

Chemical phylogeny

In the past, khat use was, generally, a fairly localized problem, but in recent years it has become more widespread. For example, in 2006, federal authorities in New York indicted several people that brought more than 25 t of khat into the United States, and in 2011 a trafficking ring was broken up in northern Virginia that involved 5 t of khat (DEA, 2006; ICE, 2012). The League of Nations considered khat use in the 1930s, and the United Nations World Health Organization considered it again in the 1960s and later in the 1970s (Document, 1979). Thus khat use and abuse have long been recognized as a problem of international dimensions.

The norepinephrine optical isomer (+)norpseudoephedrine (now termed cathine; see Fig. 1 for structure) was first isolated from the khat plant in 1930 (Wolfes, 1930). It was independently isolated by others (Alles et al., 1961; Ristic and Thomas, 1962), and the former investigators found cathine to be a mild central stimulant. However, shortly afterward it was demonstrated that cathine was not a central stimulant as potent as 'khat extract' (Friebel and Brilla, 1963). This led to speculation that khat might contain other stimulant component(s). In 1975, a UN working group isolated (−)α-aminopropiophenone from fresh khat leaves and termed the substance *cathinone* (Document, 1975) (see Fig. 1). In 1979–1980, the UN made available to groups of investigators synthetic (±)cathinone and its individual optical isomers. It might be noted that, initially, the term *cathinone* was reserved for the naturally-occurring (−)cathinone (hence, some of the early literature might be confusing); today, cathinone refers to the racemate unless an isomer is specifically identified.

Several studies showed that (−)cathinone is more potent than (±) cathinone or cathine as a locomotor stimulant in rodents (Knoll, 1979; Rosecrans et al., 1979; Yanagita, 1979; Glennon and Showalter, 1981). As with its structural cousin, amphetamine, (−)cathinone produced hyperthermia in rabbits that could be blocked by the dopamine (DA) antagonist haloperidol (Kalix, 1980). Interestingly, van der Schoot et al. had investigated the hyperthermia effects (rabbit) and locomotor actions (mice) of a large number of random amphetamine analogs nearly 20 years earlier (van der Schoot et al., 1962) Specific optical isomers were not indicated and it must be assumed that racemates were examined. What we now know as cathinone was coincidentally shown to be a locomotor stimulant in 1962.

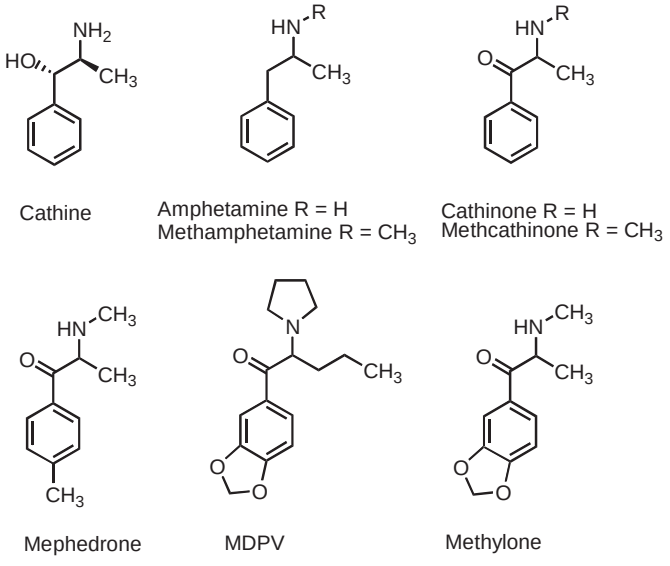

Fig. 1. The structural relationships between cathine, amphetamine, methamphetamine, cathinone, methcathinone, mephedrone, MDPV, and methylone (MDMC).

Various other studies over the ensuing years concluded that, like amphetamine, cathinone and several related cathinone analogs are DA releasing agents (Kalix and Glennon, 1986; Glennon et al., 1987), that both optical isomers of cathinone substitute for training drug in rats trained to discriminate (+)amphetamine from vehicle, that stimulus generalization could be blocked by haloperidol (Glennon et al., 1984a), and that cathinone itself could be used as a training drug in drug discrimination studies using rats as subjects (Glennon et al., 1984a, 1984b; Schechter and Glennon, 1985). In these, and other, investigations *S*(−)cathinone was found more potent that *R*(+)cathinone just as *S*(+)amphetamine is more potent than *R*(−)amphetamine.

Several investigators referred to cathinone as a "*naturally-occurring amphetamine*", but some in the pharmacological community argued that the more potent optical isomer of amphetamine is the (+)-isomer whereas the more potent isomer of cathinone is the (−)-isomer. The counter-argument was that the more potent isomer of both agents possesses an *S* absolute configuration. Because one of the few structural alterations of the amphetamine molecule that resulted in increased stimulant potency is *N*-monomethylation (i.e., methamphetamine), the *N*-monomethyl analog of cathinone was prepared, evaluated, and termed *methcathinone* (Glennon et al., 1987). Methcathinone might be considered the first "*synthetic cathinone*". Methcathinone was found at least as potent as methamphetamine as a locomotor stimulant, as a DA releasing agent, and in tests of stimulus generalization using rats trained to discriminate (+)amphetamine from saline vehicle; *S*(−) methcathinone was found to be more potent than its *R*(+)enantiomer (Glennon et al., 1995). Rats were subsequently trained to discriminate *S*(−)methcathinone from vehicle and the stimulus was potently blocked by haloperidol (Dal Cason et al., 1997). All evidence suggested that *S*(−)methcathinone was a potent central stimulant acting through a dopaminergic mechanism.

The substance now known as *methcathinone*, though not called by this name at the time, was synthesized by Roger Adams and his students in 1928 (Hyde et al., 1928), later patented by Parke-Davis as an analeptic agent (L'Italien et al., 1957) and examined by van der Schoot et al. (1962) as a locomotor stimulant. According to a USSR Interior Ministry report released in 1989, ephedrone – now realized as being equivalent to methcathinone – "*surfaced* [in the former Soviet Union] *for the first time in 1982*" (Savenko et al., 1989). However, this information was not widely available until 1991 (Zhingel et al., 1990). Hence, it might be said that methcathinone has been re-discovered several times over.

Another early synthetic cathinone was methylenedioxymethcathinone (MDMC, methylone) (see Fig. 1 for structure). The agent was independently prepared by two groups of investigators in the mid-1990s (Jacob and Shulgin, 1996; Dal Cason et al., 1997), and found to be about six times less potent than racemic methcathinone in tests of stimulus generalization using (+)amphetamine-trained rats (Dal Cason et al., 1997).

Relatively little interest was shown in cathinone analogs until 2010 when Iversen submitted a report to the UK Home Office entitled "*Consideration of the Cathinones*" (Iversen, 2010a, 2010b). Indeed, mephedrone use in the UK and Europe preceded MDPV use in the US. At about this time, bath salts were becoming a problem in the US, leading in 2011 to Schedule I status of these compounds (Fig. 1). Since then attention has been paid to drug combinations known as "bath salts", which may include methylenedioxypyrovalerone (MDPV), mephedrone, and methylone (MDMC) either alone, in combination with one another, or combined with other chemically related or unrelated drugs (Spiller et al., 2011; Shanks et al., 2012; Marinetti and Antonides, 2013).

Mephedrone is the *para*-methyl analog of methcathinone or the beta-keto analog of *para*-methylmethamphetamine (a relatively weak central stimulant with known abuse properties); methylone (MDMC)