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Abuse-related neurochemical and behavioral effects of cathinone and 4-methylcathinone stereoisomers in rats

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Abstract
Cathinone and many of its analogs produce behavioral effects by promoting transporter-mediated release of the monoamine neurotransmitters dopamine, norepinephrine and/or serotonin. Stereoselectivity is one determinant of neurochemical and behavioral effects of cathinone analogs. This study compared effectiveness of the *S*(−) and *R*(+) enantiomers of cathinone and 4-methylcathinone to produce in vitro monoamine release and in vivo abuse-related behavioral effects in rats. For neurochemical studies, drug effects were evaluated on monoamine release through dopamine, norepinephrine, and serotonin transporters (DAT, NET and SERT, respectively) in rat brain synaptosomes. For behavioral studies, drug effects were evaluated on responding for electrical brain stimulation in an intracranial self-stimulation (ICSS) procedure. The cathinone enantiomers differed in potency [*S*(−)>*R*(+)], but both enantiomers were >50-fold selective at promoting monoamine release through DAT vs. SERT, and both enantiomers produced ICSS facilitation. The 4-methylcathinone enantiomers also differed in potency [*S*(−)>*R*(+)]; however, in neurochemical studies, the decrease in potency from *S*(−) to *R*(+)4-methylcathinone was less for DAT than for SERT, and as a result, DAT vs. SERT selectivity was greater for *R*(+) than for *S*(−)4-methylcathinone (4.1- vs. 1.2-fold). Moreover, in behavioral studies, *S*(−)4-methylcathinone produced only ICSS depression, whereas *R*(+)4-methylcathinone produced ICSS facilitation. This study provides further evidence for stereoselectivity in neurochemical and behavioral actions of cathinone analogs.

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More importantly, stereoselective 4-methylcathinone effects on ICSS illustrate the potential for diametrically opposite effects of enantiomers in a preclinical behavioral assay of abuse potential.

1. Introduction

4-Methyl-*N*-methylcathinone (mephedrone) is a para-methyl methcathinone analog that has appeared in Europe and the United States as a common component of designer drug formulations known by names such as "bath salts" or "research chemicals". Concern over abuse of these compounds has stimulated research to investigate mechanisms that underlie their abuse liability, and this work has led to three general conclusions. First, like its parent compound methcathinone, and like more commonly abused stimulants such as methamphetamine, mephedrone functions as a substrate at dopamine (DA), norepinephrine (NE) and serotonin (5HT) transporters (DAT, NET and SERT, respectively) and promotes activity-independent neuronal release of DA, NE and 5HT both in vitro and in vivo (Rothman et al., 2001; Baumann et al., 2012). Second, the abuse potential of monoamine releasers appears to depend in part on their selectivity to promote release via DAT vs. SERT, such that DAT-selective compounds possess higher abuse potential than non-selective or SERT-selective compounds (Wee et al., 2005; Bauer et al., 2013; Negus and Miller, 2014). Consistent with this general correlation, racemic mephedrone is a relatively non-selective substrate at DAT and SERT in comparison to more DAT-selective compounds such as methcathinone and methamphetamine (Rothman et al., 2001; Baumann et al., 2012; Cozzi et al., 2013), and relative to DAT-selective releasers, mephedrone produces more variable reinforcing effects across subjects in assays of self-administration (Aarde et al., 2013; Motbey et al., 2013; Creehan, Vandewater, and Taffe 2015), and weaker evidence for abuse-related effects in assays of intracranial self-stimulation (ICSS) (Bonano et al., 2014; Robinson et al., 2012).

Finally, a growing body of literature suggests that stereochemistry is a determinant of abuse-related effects of monoamine releasers. Specifically, methcathinone, methamphetamine, and many of their analogs possess a single chiral carbon atom (the α carbon; Figure 1), and the *S* enantiomer of these compounds is typically more potent and/or effective than the *R* enantiomer to produce abuse-related behavioral effects in assays of drug self-administration, drug discrimination or ICSS (Balster and Schuster, 1973; Bauer et al., 2013; Glennon et al., 1984; Johanson and Schuster, 1981; Yanagita, 1986) and to promote DA release via DAT (Rothman et al., 2001, 2003). However, recent studies suggest a potentially more nuanced role for stereochemistry in abuse-related effects of mephedrone. Specifically, the *R*(+) enantiomer of mephedrone is more effective than the *S*(−) enantiomer to produce locomotor activation, conditioned place preference, and facilitation of ICSS in rats (Gregg et al., 2015). Neurochemical evidence suggests that this apparent inversion of stereochemistry results from an unusual stereoselectivity not only in potency, but also in selectivity as a substrate at DAT vs. SERT. Thus, *R*(+) mephedrone is slightly more potent than its *S*(−) enantiomer in promoting monoamine release via DAT but much less

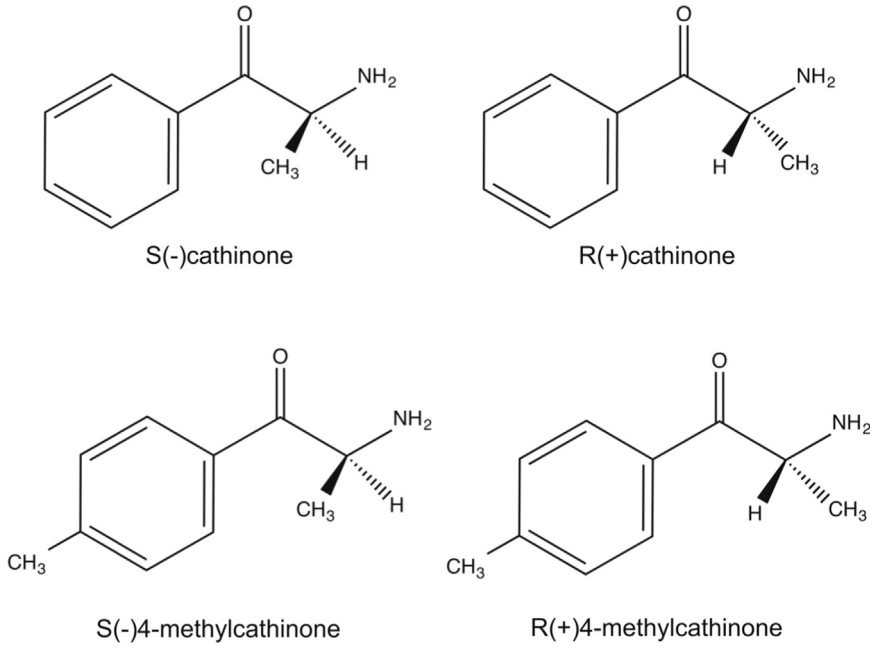

Figure 1 Chemical structures of *S*(−) and *R*(+) enantiomers of cathinone and 4-methylcathinone tested in this study.