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Locomotor and reinforcing effects of pentedrone, pentylone and methylone in rats

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ABSTRACT

The broad diversity of synthetic cathinone psychostimulant drugs that are available to users complicates research efforts to provide understanding of health risks. Second generation cathinones pentedrone and pentylone are distinguished from each other by the 3,4-methylenedioxy structural motif (which distinguishes methamphetamine from 3,4-methylenedioxymethamphetamine) and each incorporates the α-alkyl chain motif contained in the transporter-inhibitor cathinones (3,4-methylenedioxypyrovalerone (MDPV), α-pyrrolidinopentiophenone (α-PVP)) but not in the monoamine releasers (mephedrone, methylone). Studies were conducted in male and female Wistar rats to compare locomotor and thermoregulatory effects of pentedrone, pentylone and methylone using an implanted radiotelemetry system. Reinforcing effects were assessed in female Wistar rats trained in the intravenous self-administration (IVSA) procedure and subjected to dose-substitution (0.025–0.3 m/gkg/inf) under a fixed-ratio 1 response contingency. Pentedrone, pentylone and methylone dose-effect curves were contrasted with those for α-PVP and α-pyrrolidinohexiophenone (α-PHP). Dose dependent increases in locomotion were observed after intraperitoneal injection of pentylone (0.5–10.0 mg/kg), pentedrone (0.5–10.0 mg/kg) or mephedrone (0.5–10.0 mg/kg) in male and female rats. The maximum locomotor effect was similar across drugs but lasted longest after pentedrone. Mean body temperature did not vary systematically more than 0.5 °C after pentedrone or pentylone in either sex. A sustained hyperthermia (0.4–0.8 °C) was observed for four hours after 10.0 mg/kg methylone in male rats. More infusions of pentedrone or pentylone were self-administered compared with methylone, but all three were less potent than α-PVP or α-PHP. These studies support the inference that second generation cathinones pentylone and pentedrone have abuse liability greater than that of methylone.

1. Introduction

Recreational use of cathinone derivative psychostimulant drugs has increased over the past decade (Madras, 2017), yet the broad diversity of the drugs that are available to users (Brunt et al., 2017; Odoardi et al., 2016) has complicated research efforts to provide understanding of various health risks (Aarde and Taffe, 2017; Angoa-Perez et al., 2017; Negus and Banks, 2017; Papaseit et al., 2017). The US DEA placed both pentedrone and pentylone under temporary Schedule I control in March of 2014 and this action was finalized in 2017 (Drug Enforcement Administration, 2014, 2017).

These compounds have been detected in forensic casework (Adamowicz et al., 2016; Elliott and Evans, 2014), and there is evidence for health threatening toxic effects of pentylone (Liakoni et al., 2015) as well as for pentedrone in combination with other cathinone derivatives (Liveri et al., 2016; Sykutera et al., 2015). Second-generation compounds such as pentylone and pentedrone have received less research attention compared with mephedrone, methylone, 3,4-methylenedioxypyrovalerone (MDPV) and α-pyrrolidinopentiophenone (α-PVP).

Although prior preclinical evidence is not comprehensive, there is evidence that pentedrone increases locomotor activity in mice (Gatch et al., 2015; Hwang et al., 2017), supports intravenous self-administration (IVSA) in male Wistar rats (Hwang et al., 2017) and substitutes for the discriminative stimulus effect of

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methamphetamine and cocaine in male rats (Gatch et al., 2015). Pentylone likewise increases locomotor activity in mice and substitutes for methamphetamine and cocaine (Gatch et al., 2015). In contrast the effects of methylone are better established. Methylone supports IVSA in both male and female rats (Aarde et al., 2015b; Creehan et al., 2015; Nguyen et al., 2017; Schindler et al., 2016; Vandewater et al., 2015; Watterson et al., 2012), facilitates intracranial self-stimulation reward in rats (Bonano et al., 2014), can condition a place preference in mice (Karlsson et al., 2014), substitutes for the discriminative stimulus effects of cocaine or methamphetamine in rats (Gatch et al., 2013) and increases body temperature and locomotor activity in rats and mice (Gatch et al., 2013; Grecco and Sprague, 2016; Kiyatkin et al., 2015; Marusich et al., 2012). Despite the fact that methylone is structurally similar to 3,4-methylenedioxymethamphetamine (MDMA) the preclinical self-administration data suggests that methylone exhibits enhanced liability for compulsive use compared with that of MDMA (Nguyen et al., 2017; Vandewater et al., 2015; Watterson et al., 2012).

The diversity of cathinone derivatives permits further investigation of the role of various substitution moieties common to both amphetamine and cathinone drugs of abuse. In this study, we investigate the 3,4-methylenedioxy motif (see Fig. 1) in the contrast of the effects of pentedrone with pentylone. This motif, when added to methamphetamine to produce MDMA, confers reduced rewarding potency and efficacy (Dalley et al., 2007; Schenk, 2009; Vandewater et al., 2015), reduced locomotor potency (Huang et al., 2012; Miller et al., 2013a), reduced efficacy to induce stereotyped, repetitive behavior and increased thermoregulatory disruption (Miller et al., 2013a). In contrast, the presence of the 3,4-methylenedioxy substitution produces no change *in vivo* in the context of the closely related, restricted transporter inhibitor cathinones α-PVP and MDPV which exhibit similar efficacy and potency on both locomotor and self-administration assays in rats (Aarde et al., 2015a). Pentedrone and pentylone also include the extended alkyl-tail carbon chain that is present on MDPV and α-PVP which may be related to the restriction of those drugs to transporter inhibition. This might predict that the 3,4-methylenedioxy motif has minimal impact on these additional compounds which lack the pyrrolidine ring of MDPV and α-PVP.

Pentedrone and pentylone exhibit negligible dopamine or norepinephrine release (Eshleman et al., 2017; Simmler et al., 2014), however some serotonin release was observed for pentylone in one of the reports and methylone is more effective than either compound (Simmler et al., 2014). The inhibition of the serotonin transporter (SERT) by pentylone is 16-fold higher than inhibition by pentedrone, similar to the 17-fold higher affinity of MDMA over methamphetamine. In addition, pentylone inhibits dopamine transporter (DAT) activity with a potency of about half that of pentedrone whereas DAT inhibition caused by methamphetamine is 17-fold higher than that of MDMA. The ratio of potencies for inhibiting the DAT versus the SERT is 54 for pentedrone, compared with 6.2 for pentylone, 3.2 for methylone, 22 for methamphetamine and 0.08 for MDMA (Simmler et al., 2013, 2014). The *in vitro* pharmacology therefore predicts that pentedrone would be significantly more potent as a locomotor stimulant or reinforcer compared with pentylone and methylone; however, the difference should be less pronounced than the potency difference between MDMA and methamphetamine. The potential of pentylone to release serotonin predicts reduced efficacy compared with pentedrone. The present study was conducted to evaluate these hypotheses *in vivo* using IVSA techniques (Aarde et al., 2013a, 2015a; Creehan et al., 2015) and a rat locomotor assay that has been used to evaluate the locomotor stimulant effects of MDPV, α-PVP, methamphetamine and MDMA (Aarde et al., 2015a; Miller et al., 2013a). In these procedures, comparison of behavioral outcomes after a range of doses can be used to infer differences in potency (the dose at which a given effect occurs) and efficacy (the maximum effect observed for any dose). These differences, if established, can then be used to support predictions or inferences about the relative abuse liability when translated to the recreational use context.

2. Methods

2.1. Subjects

Male (N = 8) and female (N = 33) Wistar (Charles River, New York) rats entered the laboratory at 10 weeks of age and were housed in humidity and temperature-controlled (23 ± 1 °C) vivaria on 12:12 h light:dark cycles. Experimental procedures took place during the animals' dark cycle. Animals had ad libitum access to food and water in their home cages. All procedures were conducted under protocols approved by the Institutional Care and Use Committees of The Scripps Research Institute and in a manner consistent with the Guide for the Care and Use of Laboratory Animals (National Research Council (U.S.). Committee for the Update of the Guide for the Care and Use of Laboratory Animals. et al., 2011).

2.2. Drugs

Drugs were dissolved in physiological saline for the i.p. or i.v. routes of administration. Pentylone HCl, pentedrone HCl, α-pyrrolidinopentiophenone HCl (α-PVP) and α-pyrrolidinohexiophenone HCl (α-PHP) were obtained from Cayman Chemical. Methylone HCl

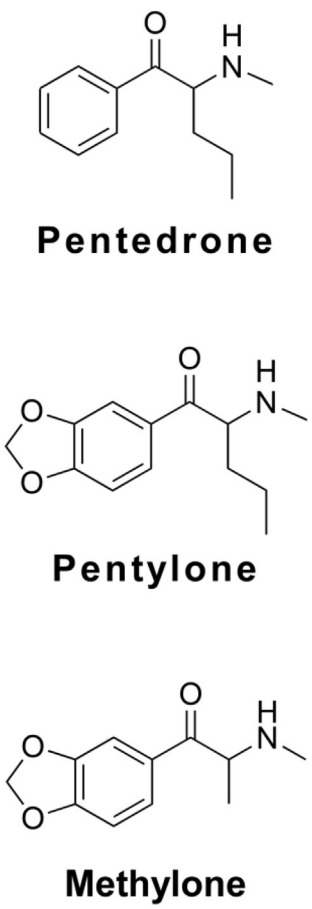

Fig. 1. Chemical structures of the substituted cathinones under investigation.

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