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Hallucinogen-like actions of 5-methoxy-*N*,*N*-diisopropyltryptamine in mice and rats

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Abstract

Few studies have examined the effects of 5-methoxy-*N*,*N*-diisopropyltryptamine (5-MeO-DIPT) in vivo. In these studies, 5-MeO-DIPT was tested in a drug-elicited head twitch assay in mice where it was compared to the structurally similar hallucinogen *N*,*N*-dimethyltryptamine (*N*,*N*-DMT) and challenged with the selective serotonin $(5\text{-HT})_{2A}$ antagonist M100907, and in a lysergic acid diethylamide (LSD) discrimination assay in rats where its subjective effects were challenged with M100907 or the 5-HT_{1A} selective antagonist WAY-100635. Finally, the affinity of 5-MeO-DIPT for three distinct 5-HT receptors was determined in rat brain. 5-MeO-DIPT, but not *N*,*N*-DMT, induced the head twitch responses in the mouse, and this effect was potently antagonized by prior administration of M100907. In rats trained with LSD as a discriminative stimulus, there was an intermediate degree (75%) of generalization to 5-MeO-DIPT and a dose-dependent suppression of response rates. These interoceptive effects were abolished by M100907, but were not significantly attenuated by WAY-100635. Finally, 5-MeO-DIPT had micromolar affinity for 5-HT_{2A} and 5-HT_{2C} receptors, but much higher affinity for 5-HT_{1A} receptors. 5-MeO-DIPT is thus effective in two rodent models of 5-HT_2 agonist activity, and has affinity at receptors relevant to hallucinogen effects. The effectiveness with which M100907 antagonizes the behavioral actions of this compound, coupled with the lack of significant antagonist effects of WAY-100635, strongly suggests that the 5-HT_{2A} receptor is an important site of action for 5-MeO-DIPT, despite its apparent in vitro selectivity for the 5-HT_{1A} receptor.

Keywords: Hallucinogens; Drug-discrimination; Head twitch response; Serotonin receptors

1. Introduction

5-methoxy-*N*,*N*-diisopropyltryptamine (5-MeO-DIPT, Fig. 1A) is a synthetic orally active hallucinogenic tryptamine analogue known by the street names "foxy" and "foxy methoxy." The synthesis and hallucinogen-like subjective effects of this compound were first described in the scientific literature (Shulgin and Carter, 1980), and expanded upon ten years later in a book which subsequently gained widespread dissemination via the internet (Shulgin and Shulgin, 1991). Since these initial descriptions, the United States Drug Enforcement Administration (DEA) has documented 5-MeO-DIPT seizures and reports of abuse in at least nine states, as well as the District of Columbia (US DEA, 2002). More recent case reports of 5-MeO-DIPT intoxication (Meatherall and Sharma, 2003; Smolinske et al., 2004; Wilson et al., 2005) suggest that abuse of this compound may be spreading beyond the geographic areas initially implicated. Similarly, a search of The American Association of Poison Control Centers Toxic Exposure Surveillance System database revealed 41 cases of 5-MeO-DIPT exposure reports to poison centers over a 15-month

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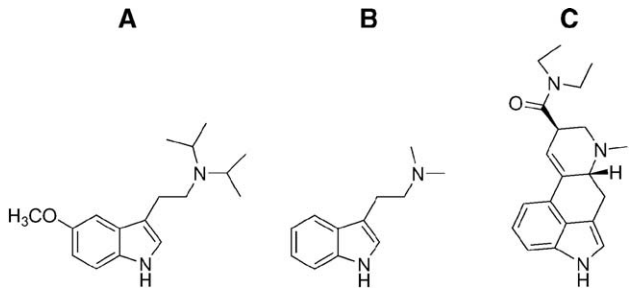

Fig. 1. Chemical structures of 5-MeO-DIPT (A. left), *N*,*N*-DMT (B. middle) and LSD (C. right). Fantegrossi et al.

period from April 2002 to the end of June 2003 (Smolinske et al., 2004).

Due to the apparent abuse and toxicity of this compound, 5-MeO-DIPT was placed temporarily into Schedule I under the Controlled Substances Act in April of 2003 (Brown, 2003), and this placement was made permanent in September of 2004 (Leonhart, 2004). Despite these aggressive regulatory measures, 5-MeO-DIPT remains available for purchase from foreign sources via the internet. Anecdotal reports from human users posted to internet sites specializing in the dissemination of drug information (for example, erowid.org and lycaeum.org) further suggest that 5-MeO-DIPT has profound psychedelic actions in man, but few studies regarding the effects of this compound in laboratory animals have been published. However, 5-MeO-DIPT has been shown to generalize to the interoceptive cue induced by *R*-(−)-1-(2,5-dimethoxy-4-methylphenyl)-2-amino-propane (DOM) in rats (Glennon et al., 1983), although the pharmacological mechanism for this effect was not explored using antagonist challenges. A later study reported that related tryptamine analogues have affinity for 5-HT_2 receptors, and suggests that these compound are likely to function as agonists due to their higher affinity for [^{3}H]4-bromo-2,5-dimethoxy-phenylisopropylamine (DOB)-labelled receptors than for [^{3}H] ketanserin-labelled sites (Lyon et al., 1988). These findings, coupled with the chemical structure of 5-MeO-DIPT and anecdotal reports of its hallucinogenic activity in man, strongly suggest that serotonin systems, specifically 5-HT_{2A} receptors (Sadzot et al., 1989), may be involved in the mediation of the behavioral and subjective effects of this compound.

In this regard, the drug-elicited head twitch response (Corne et al., 1963; Corne and Pickering, 1967) is a selective behavioral model for 5-HT_2 agonist activity in the rodent, and several previous studies have established that direct and indirect 5-HT agonists induce this effect (Peroutka et al., 1981; Colpaert and Janssen, 1983; Green et al., 1983; Goodwin and Green, 1985; Darmani et al., 1990a,b, 1992; Fantegrossi et al., 2004). Further, 5-HT_2 receptor antagonists selectively block head twitch behavior (Lucki et al., 1984; Handley and Singh, 1986; Fantegrossi et al., 2004), and the potency with which they do so is highly correlated with the antagonist's affinity for 5-HT_2 receptors (Peroutka et al., 1981; Ortmann et al., 1982). Similarly, the strong correlation between discriminative stimuli in nonverbal species and subjective effects reported by humans (Schuster and Johanson, 1988; Sanger et al., 1994; Brauer et al., 1997) allows for a useful characterization of the interoceptive cues produced by psychedelic drugs using drug discrimination procedures in laboratory rodents. The discriminative stimulus properties of hallucinogens such as mescaline, DOM and lysergic acid diethylamide (LSD, Fig. 1C) have been extensively investigated in several different animal species and it has been shown that, in agreement with studies in humans, these drugs generalize with one another (Winter, 1978; Glennon et al., 1983; Fiorella et al., 1995a). Furthermore, antagonist correlation analysis has determined that the stimulus effects of phenylisopropylamine and indolealkylamine hallucinogens are mediated by agonist activity at 5-HT_{2A} receptors (Fiorella et al., 1995b) and possibly modulated by agonist activity at 5-HT_{2C} receptors (Fiorella et al., 1995c).

Thus, in order to compare potency and effectiveness of 5-MeO-DIPT with the more familiar tryptamine hallucinogens, we established dose–effect functions for 5-MeO-DIPT and the structurally similar psychedelic *N*,*N*-dimethyltryptamine (DMT, Fig. 1B) in the head twitch assay in mice. Antagonist studies were then conducted with the selective 5-HT_{2A} antagonist (+)-(2,3-dimethoxyphenyl)-1-[2-(4-fluorophenylethyl)]-4-piperidine-methanol (M100907, formerly MDL100907) in order to gauge the involvement of 5-HT_{2A} receptors in the induction of this behavior. A parallel series of drug discrimination experiments was conducted in rats in order to characterize the similarity of the discriminative stimulus effects of 5-MeO-DIPT with those of LSD. The effects of M100907 and the selective 5-HT_{1A} antagonist *N*-(2-(1-(4-(2-methoxyphenyl)-1-piperazinyl)ethyl)-*N*-(2-pyridyl) cyclohexane-carboxamide (WAY-100635) on LSD-appropriate responding were also tested in rats receiving an active dose of 5-MeO-DIPT. Finally, binding of 5-MeO-DIPT to 5-HT_{1A}, 5-HT_{2A} and 5-HT_{2C} receptors was characterized in rat brain using a competition binding technique.

2. Methods

All studies were carried out in accordance with the Declaration of Helsinki and with the Guide for Care and Use of Laboratory animals as adopted and promulgated by the National Institutes of Health. Experimental protocols were approved by the Animal Care and Use Committees at the University of Michigan and the State University of New York at Buffalo.

2.1. Animals — drug-elicited head twitch response

Male NIH Swiss mice (Harlan Sprague Dawley Inc., Indianapolis, IN) weighing approximately 20–30 g were housed 12 animals per 44.5×22.3×12.7 cm Plexiglas cage and used in drug-elicited head twitch experiments. Mice were housed in a temperature-controlled room at the University of Michigan that was maintained at an ambient temperature of 22±2 °C at 45–50% humidity. Lights were set to a 12-h light/dark cycle. Animals were fed Lab Diet rodent chow (Laboratory Rodent Diet #5001, PMI Feeds, Inc., St. Louis, MO) and water ad