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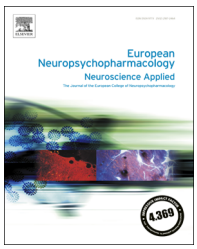

Receptor interaction profiles of novel psychoactive tryptamines compared with classic hallucinogens

Anna Rickli[a], Olivier D. Moning[a], Marius C. Hoener[b], Matthias E. Liechti[a,*]

[a]*Psychopharmacology Research, Division of Clinical Pharmacology and Toxicology, Department of Biomedicine, University Hospital Basel and University of Basel, Basel, Switzerland*
[b]*Neuroscience Research, pRED, Roche Innovation Center Basel, F. Hoffmann-La Roche Ltd., Basel, Switzerland*

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Abstract
The present study investigated interactions between the novel psychoactive tryptamines DiPT, 4-OH-DiPT, 4-OH-MET, 5-MeO-AMT, and 5-MeO-MiPT at monoamine receptors and transporters compared with the classic hallucinogens lysergic acid diethylamide (LSD), psilocin, *N,N*-dimethyltryptamine (DMT), and mescaline. We investigated binding affinities at human monoamine receptors and determined functional serotonin (5-hydroxytryptamine [5-HT]) 5-HT_{2A} and 5-HT_{2B} receptor activation. Binding at and the inhibition of human monoamine uptake transporters and transporter-mediated monoamine release were also determined. All of the novel tryptamines interacted with 5-HT_{2A} receptors and were partial or full 5-HT_{2A} agonists. Binding affinity to the 5-HT_{2A} receptor was lower for all of the tryptamines, including psilocin and DMT, compared with LSD and correlated with the reported psychoactive doses in humans. Several tryptamines, including psilocin, DMT, DiPT, 4-OH-DiPT, and 4-OH-MET, interacted with the serotonin transporter and partially the norepinephrine transporter, similar to 3,4-methylenedioxymethamphetamine but in contrast to LSD and mescaline. LSD but not the tryptamines interacted with adrenergic and dopaminergic receptors. In conclusion, the receptor interaction profiles of the tryptamines predict hallucinogenic effects that are similar to classic serotonergic hallucinogens but also MDMA-like psychoactive properties.

*Correspondence to: Division of Clinical Pharmacology and Toxicology, University Hospital Basel, Hebelstrasse 2, Basel CH-4031, Switzerland. Tel.: +41 61 328 68 68; fax: +41 61 265 45 60.
E-mail address: matthias.liechti@usb.ch (M.E. Liechti).

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1. Introduction

Classic or serotonergic hallucinogens can be grouped into different chemical groups, including tryptamines (e.g., psilocin and *N,N*-dimethyltryptamine [DMT]), ergolines (lysergic acid diethylamide [LSD]), and phenethylamines (e.g., mescaline). Psychoactive tryptamines are naturally found in toads, plants, and mushrooms. However, many synthetic tryptamine derivatives have been synthesized and are recreationally used as novel psychoactive substances (Araujo et al., 2015; EMCDDA, 2014; Helander et al., 2014; Kamour et al., 2014; Shulgin and Shulgin, 1997; Tittarelli et al., 2015; Winstock et al., 2014). Tryptamines share their core structure with the neurotransmitter serotonin (5-hydroxytryptamine [5-HT]). The psychoactive effects of hallucinogens, including those of tryptamines, are thought to be mediated mainly by the 5-HT_{2A} receptor (Glennon et al., 1984; Nichols, 2004; Titeler et al., 1988; Vollenweider et al., 1998) but may also be modulated by interactions with other targets, including other 5-HT receptors, monoamine transporters, and trace amine-associated receptors (Baumeister et al., 2014; Bunzow et al., 2001; Cozzi et al., 2009; Fantegrossi et al., 2006; McKenna et al., 1990; Nagai et al., 2007; Nichols, 2004; Ray, 2010). Structural alterations of tryptamines have been shown to result in different pharmacological and psychoactive profiles (Araujo et al., 2015; McKenna et al., 1990; Repke et al., 1985; Shulgin and Shulgin, 1997; Tittarelli et al., 2015; Trachsel et al., 2013). For example, compounds that have no substitutions or a 4-hydroxyl group (e.g., DMT or psilocin, respectively; Figure 1) produce hallucinogenic effects with relative low potency in man (Repke et al., 1985). Psilocin is orally psychoactive above 5–10 mg, and DMT is active at parenteral doses of 20–100 mg (Araujo et al., 2015; Shulgin and Shulgin, 1997; Strassman et al., 1994; Studerus et al., 2011; Tittarelli et al., 2015). In contrast, a 5-methoxy group, such as in 5-MeO-AMT (Figure 1), resulted in greater compound potency, with subjective effects at 1–5 mg doses, more stimulant-type activation, and less visual perceptual alterations (Repke et al., 1985). Different *N*-substitutions also influenced *in vivo* potency (Nichols et al., 2015; Repke et al., 1985). The pharmacological profiles of many tryptamines have been studied previously at selected targets (Blough et al., 2014; Gatch et al., 2011; McKenna et al., 1990; Nichols et al., 2015; Repke et al., 1985; Shulgin and Carter, 1980), and new and pharmacologically unknown tryptamine derivatives are constantly emerging on the illicit drug market (Araujo et al., 2015; Corkery et al., 2012; EMCDDA, 2014; Greene, 2013; Helander et al., 2014; Tittarelli et al., 2015). Because small changes in molecular structure can alter the pharmacology of these novel designer drugs, studying the *in vitro* receptor interaction profiles of these novel substances is important. Such data can help predict psychotropic effects and acute clinical toxicity. Therefore, we assessed the receptor interaction profiles of a series of classic and novel tryptamines at human monoamine receptors and assessed 5-HT_{2A} receptor activation. LSD and mescaline were included for comparison. Tryptamines have also been shown to interact with membrane monoamine transporters to inhibit their function or release monoamines through the transporter (Araujo et al., 2015; Cozzi et al., 2009; Nagai et al., 2007), similar to 3,4-methylenedioxymethamphetamine (MDMA) and many other novel psychoactive substances (Rickli et al., 2015a; Simmler et al., 2013; Simmler et al., 2014a, 2014b). Therefore, inhibition of the norepinephrine (NE), dopamine (DA), and 5-HT transporters (NET, DAT, and SERT, respectively) and the release of NE, DA, and 5-HT were also investigated. MDMA was included as a comparator in these assays.

The present study included recreationally used tryptamines (Araujo et al., 2015; EMCDDA, 2014; Greene, 2013; Schmidt et al., 2011; Tittarelli et al., 2015), including *N,N*-diisopropyltryptamine (DiPT), 4-hydroxy-*N,N*-diisopropyltryptamine (4-OH-DiPT), 4-hydroxy-*N*-methyl-*N*-ethyltryptamine (4-OH-MET), 5-methoxy-α-methyltryptamine (5-MeO-AMT), and 5-methoxy-*N*-methyl-*N*-isopropyltryptamine (5-MeO-MiPT; Figure 1). DiPT is a ring-unsubstituted tryptamine, similar to DMT. DiPT fully substituted for DMT in discrimination studies (Gatch et al., 2011) but unlike DMT reportedly induces auditory and not visual alterations in humans (Blough et al., 2014). DiPT is psychoactive at doses of 20–100 mg, with effects that last 4–8 h (Shulgin and Carter, 1980; Tittarelli et al., 2015).

DiPT is an agonist at rat and human 5-HT_{2A} receptors and also blocks the rat and human SERT (Blough et al., 2014; Cozzi et al., 2009; Gatch et al., 2011; Nagai et al., 2007). However, interactions with other receptors have not yet been studied.

4-OH-DiPT has been detected in the urine of substance users (Pichini et al., 2008), and a series of 4-OH-MET intoxications has recently been reported (Helander et al., 2013; Taljemark and Johansson, 2012). The subjective effects of these 4-substituted tryptamines that are used at oral doses of 10–20 mg are reportedly similar to those of psilocybin and last 2–6 h. The

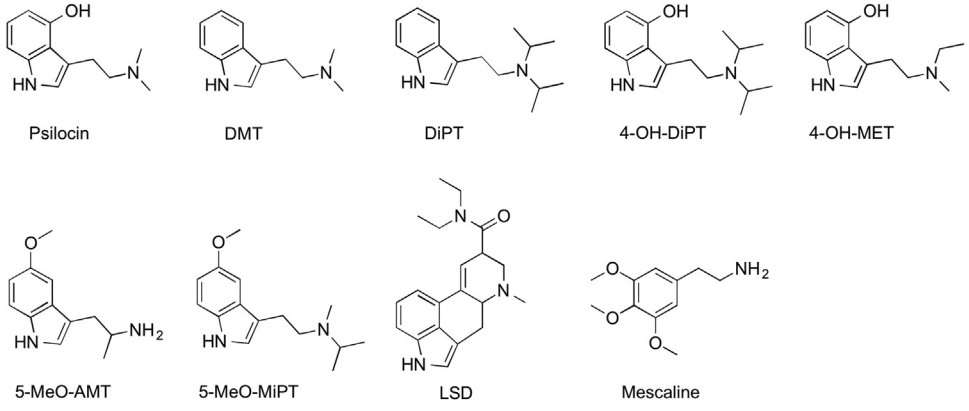

Figure 1 Chemical structures of tryptamines, LSD, and mescaline.