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# Modulatory effect of the 5-HT1A agonist buspirone and the mixed non-hallucinogenic 5-HT1A/2A agonist ergotamine on psilocybin-induced psychedelic experience

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**Abstract**
The mixed serotonin (5-HT) 1A/2A/2B/2C/6/7 receptor agonist psilocybin dose-dependently induces an altered state of consciousness (ASC) that is characterized by changes in sensory perception, mood, thought, and the sense of self. The psychological effects of psilocybin are primarily mediated by 5-HT2A receptor activation. However, accumulating evidence suggests that 5-HT1A or an interaction between 5-HT1A and 5-HT2A receptors may contribute to the overall effects of psilocybin. Therefore, we used a double-blind, counterbalanced, within-subject design to investigate the modulatory effects of the partial 5-HT1A agonist buspirone (20 mg p.o.) and the non-hallucinogenic 5-HT2A/1A agonist ergotamine (3 mg p.o.) on psilocybin-induced (170 μg/kg p.o.) psychological effects in two groups ($n=19$, $n=17$) of healthy human subjects. Psychological effects were assessed using the Altered State of Consciousness (5D-ASC) rating scale. Buspirone significantly reduced the 5D-ASC main scale score for Visionary Restructuralization (VR) ($p<0.001$), which was mostly driven by a reduction of the VR item cluster scores for elementary and complex visual hallucinations. Further, buspirone also reduced the main scale score for Oceanic Boundlessness (OB) including derealisation and depersonalisation phenomena at a trend level ($p=0.062$), whereas ergotamine did not show any effects on the psilocybin-induced 5D-ASC main scale scores. The present finding demonstrates that buspirone exerts inhibitory effects on psilocybin-induced effects, presumably via 5-HT1A receptor activation, an interaction between 5-HT1A and 5-HT2A receptors, or both. The data suggest that the modulation of 5-HT1A receptor activity may be

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a useful target in the treatment of visual hallucinations in different psychiatric and neurological diseases.


## 1. Introduction

Serotonergic hallucinogens or psychedelic drugs such as psilocybin (4-phosphoryloxy-N,N-dimethyltryptamine), DMT (N,N-dimethyltryptamine), and LSD (lysergic acid diethylamide) produce an altered state of consciousness (ASC) that is characterized by profound changes in sensory perception, emotion, thought, and the sense of self (Geyer and Vollenweider, 2008; Studerus et al., 2011). Psilocybin is the main psychoactive principle of the group of hallucinogenic fungi, commonly known as magic mushrooms (Hofmann, 1968).

Since the 1990s, a series of studies have been conducted in humans to identify the neurophysiological and molecular mechanism of psilocybin-induced ASC, including investigations into the underpinnings of perceptual alterations such as hallucinations, changes in thought, and alterations in the experience of self (Geyer and Vollenweider, 2008; Lebedev et al., 2015; Vollenweider and Geyer, 2001; Vollenweider, 2001). More recent studies have focused on the neuronal substrates of the effect of psilocybin on cognition (Carter et al., 2005; Quednow et al., 2012; Umbricht et al., 2003; Vollenweider et al., 2007), emotion regulation (Bernasconi et al., 2014; Kometer et al., 2011; Kraehenmann et al., 2014, 2015; Schmidt et al., 2013), and social interaction (Preller et al., 2015), while some studies have begun to re-evaluate the clinical potential of psilocybin for example in the treatment of anxiety and depression in terminally ill cancer patients (Gasser et al., 2015; Grob et al., 2011; Majić et al., 2015; Vollenweider and Kometer, 2010).

In humans, psilocybin is rapidly dephosphorylated into the psychoactive metabolite psilocin (4-hydroxy-N,N-dimethyltryptamine) (Hasler et al., 1997) which acts as an agonist at 5-HT1A, 5-HT2A, 5-HT2B, 5-HT2C, 5-HT6, and 5-HT7 receptors (Nichols, 2004; PDSP database https://pdspdb.unc.edu/html/pdspV2/). There is converging evidence from human and animal studies that the core psychological effects of psilocybin are primarily mediated via 5-HT2A receptor activation, although serotonergic hallucinogens interact with multiple serotonin receptor sites (González-Maeso et al., 2008, 2007; Halberstadt et al., 2011; Vollenweider et al., 1998). Specifically, the 5-HT2A antagonist ketanserin blocked the psilocybin-induced subjective effects including hallucinations (Carter et al., 2007; Kometer et al., 2012; Vollenweider et al., 1998) and the disruption of sensory gating as indexed by prepulse inhibition (PPI) in humans (Quednow et al., 2012; Vollenweider et al., 2007). Furthermore all serotonergic hallucinogens also induce a head-twitch response (HTR) in rodents that is blocked by highly selective 5-HT2A receptor antagonists (González-Maeso et al., 2007; Halberstadt and Geyer, 2010; Halberstadt et al., 2011; Hanks and González-Maeso, 2013). In contrast to this, non-hallucinogenic 5-HT2A/1A receptor agonists such as ergotamine or R-lisuride do not induce the HTR in rodents (González-Maeso et al., 2007; Hanks and González-Maeso, 2013) and also activate distinct 5-HT2A mediated signalling in cortical neurons. Moreover, R-lisuride blocked the LSD-induced HTR and pyramidal cell activation in somatosensory cortices in mice (González-Maeso et al., 2007).

Although the prevailing view is that 5-HT2A receptor activation is responsible and necessary for many of the psychedelic effects of psilocybin in humans (González-Maeso et al., 2007; Vollenweider et al., 1998), other data suggest that activation of 5-HT1A receptors by serotonergic hallucinogens may also contribute to their subjective and behavioural effects, either directly or through functional interaction with 5-HT2A receptors (Halberstadt et al., 2011; Krebs and Geyer, 1994; Krebs-Thomson and Geyer, 1998). For example, it is well established that the DOI-induced HTR can be blocked by 5-HT1A receptors agonists such as 8-OH-DPAT, buspirone, ipsapirone, and flesinoxan (Dursun and Handley, 1993; Schreiber et al., 1995). Moreover, several 5-HT1A agonists including buspirone have been shown to increase PPI in multiple strains of mice (Geyer, 1999), although opposite effects on PPI have also been reported in rats (Geyer et al., 2001). In addition, isobolographic analysis of the locomotion suppressing effects of hallucinogens in rats suggests that at a functional level, 5-HT1A and 5-HT2 receptors interact antagonistically in the modulation of locomotor activity (Krebs-Thomson and Geyer, 1998).

While a number of behavioural paradigms in animals suggest that 5-HT1A receptor agonists produce opposite effects on 5-HT2A receptor mediated behaviour induced by hallucinogens, the role of 5-HT1A receptors in psychedelic symptom formation in humans is hardly known. The only human study that has explored the potential contribution of the 5-HT1A receptor system to psychedelic symptom formation reported that manipulation of 5-HT1A receptor system by the partial 5-HT1A receptor antagonist pindolol increased the hallucinogenic effects of DMT about two to three fold in healthy human subjects (Strassman, 1996). Taken together, the accumulating evidence from these behavioural animal studies suggests that the 5-HT1A receptor system may have a modulatory role on psychedelic symptom formation and proposes that 5-HT1A receptor agonists such as buspirone or non-hallucinogenic 5-HT1A/2A receptor agonists such ergotamine might reduce or block psilocybin-induced psychedelic effects in humans.

To test this hypothesis, we studied whether pre-treatment with the partial 5-HT1A agonist buspirone or the non-hallucinogenic 5-HT2A/1A receptor agonist ergotamine modulates the subjective effects of psilocybin including alterations in perception, emotions, thought, and the sense of self in healthy human subjects. Psilocin binds with high affinity to 5-HT1A (Ki 49-567 nM, human cloned receptor, using 3H-8-OH-DPAT as comparator, Blair et al. (2000)) and 5-HT2A receptors (Ki 107 nM, human cloned receptor using 3H-Ketanserin, PDSP database https://pdspdb.unc.edu/html/pdspV2). Buspirone is a partial agonist at