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HOT TOPICS

Plasma psilocin critically determines behavioral and neurobiological effects of psilocybin

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Psilocybin is a psychedelic compound that occurs naturally in "magic mushrooms". It is emerging as a promising drug for several brain disorders, including depression and anxiety [1]. Whereas traditional pharmacological treatment of depression and anxiety requires daily drug intake, a single dose of psilocybin has in preliminary reports provided beneficial effects with both rapid onset and long-lasting duration. After intake, psilocybin is rapidly converted into the psychoactive metabolite psilocin [2]. Given psilocybin's potential as a transnosological treatment modality (i.e., efficacy for more than one brain disorder), it is important to understand psilocin-dependent changes in neurobiology, psychedelic phenomenology, and clinical outcomes, since this may help optimize psilocybin treatment strategies and ultimately lead to a novel pharmacotherapy.

Psilocin is an agonist at several serotonin (5-HT) receptors, including 1A, 2A, and 2C receptors [3]. A study in humans showed that pretreatment with the serotonin 2A receptor (5-HT2AR) antagonist ketanserin effectively prevented psychedelic effects of psilocybin, establishing that engagement of the 5-HT2AR is a key mode of action [4]. Consequently, psilocin stimulation of cerebral 5-HT2ARs is considered a prime candidate molecular mechanism for psychedelic effects, but the extent to which psilocin stimulates cerebral 5-HT2ARs in the living human brain and how this relates to subjective psychedelic effects has only recently been discovered by our group [5].

In this study, we conducted a positron emission tomography (PET) 5-HT2AR occupancy study, using the 5-HT2AR agonist radioligand [^{11}C]Cimbi-36. Eight healthy individuals underwent a baseline [^{11}C]Cimbi-36 PET scan and one ($n = 3$) or two ($n = 5$) [^{11}C]Cimbi-36 PET rescans after intake of peroral psilocybin. The psychoactive dose of administered psilocybin spanned from a low dose (3 mg) to a high and strongly psychedelic dose (30 mg). Since plasma psilocin level (PPL) and subjective drug intensity (SDI) also were determined during the PET scans, we could evaluate the associations between cerebral 5-HT2AR occupancy, psilocin (PPL), and subjective effects (SDI).

With these doses and within 1–3 h after intake, psilocybin induced 5-HT2AR occupancies between 43 and 72% and associated subjective effects (40–100% of scale maximum). PPL and SDI displayed highly similar time courses and were positively correlated ($R^2 = 0.35$). We also observed a close positive association of PPL with 5-HT2AR occupancy ($R^2 = 0.9$), a relation which conformed to a single-site binding model. 5-HT2AR occupancy and SDI also correlated positively ($R^2 = 0.8$). Interestingly, our results indicate that at 5-HT2AR occupancies up to ~15%, no perceptual subjective effects occur. Our findings demonstrate that PPL is a key determinant of both the magnitude of 5-HT2AR occupancy and the overall psychedelic experience.

Psilocybin research is undergoing a renaissance, and psilocybin therapy is poised to become a valuable treatment for several neuropsychiatric disorders. We believe that future psilocybin clinical trials will benefit from measuring PPL since this would allow for an objective assessment of the individual contribution of pharmacological (psilocin) vis-à-vis non-pharmacological factors. This can lead to optimized and perhaps also individualized treatment regimens.

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AUTHOR CONTRIBUTIONS

MKM and GMK wrote the present manuscript and were the foremost contributors to Madsen et al. [5].

ADDITIONAL INFORMATION

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