

PSILOCYBIN, an indoleamine hallucinogen, produces a psychosis-like syndrome in humans that resembles first episodes of schizophrenia. In healthy human volunteers, the psychotomimetic effects of psilocybin were blocked dose-dependently by the serotonin-2A antagonist ketanserin or the atypical antipsychotic risperidone, but were increased by the dopamine antagonist and typical antipsychotic haloperidol. These data are consistent with animal studies and provide the first evidence in humans that psilocybin-induced psychosis is due to serotonin-2A receptor activation, independently of dopamine stimulation. Thus, serotonin-2A overactivity may be involved in the pathophysiology of schizophrenia and serotonin-2A antagonism may contribute to therapeutic effects of antipsychotics *NeuroReport* 9: 3897–3902

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Psilocybin induces schizophrenia-like psychosis in humans via a serotonin-2 agonist action

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Introduction

The dopamine (DA) hypothesis of schizophrenia has emphasized that a dopaminergic dysbalance is critical in the pathophysiology and treatment of schizophrenia. Increasing evidence, however, suggests that serotonin (5-HT) may also be implicated. Support for an involvement of the serotonin system stems from observations that schizophrenia patients show alterations in cortical serotonin receptor binding; novel atypical antipsychotics have potent antagonistic action at 5-HT₂ receptors; and classic indoleamine hallucinogens, which interfere with the serotonin system, can elicit schizophrenia-like symptoms in humans (for a review see Ref. 1).

Psilocybin (O-phosphoryl-4-hydroxy-N, N-dimethyltryptamine) in particular, a natural indoleamine hallucinogen, has been reported in extensive studies to produce a clinical syndrome that resembles in certain respects the first manifestation of schizophrenic decompensation.^{1,2} Ego-disorders,^{2,3} affective changes,² loosened associations⁴ and perceptual alterations are especially common features of psilocybin-induced and early acute schizophrenic stages.^{1,2,5,6} Similar findings have also been reported for the structurally related indoleamine hallucinogen lysergic acid diethylamide (LSD), when the comparison involved early, as opposed to chronic,

schizophrenics.⁷ Consistent with this suggested clinical similarity, we recently found that psilocybin in normal subjects produced a marked prefrontal activation associated with ego- and thought disorder³ comparable to that seen in acutely ill unmedicated or first episode schizophrenics.⁸

After ingestion, psilocybin is immediately dephosphorylated to psilocin (4-hydroxy-N,N-dimethyltryptamine),⁹ which is closely related in chemical structure to serotonin (5-hydroxytryptamine, 5-HT). Psilocybin and LSD also share similarities in psychological effects in humans and in neurochemical actions in animals with phenalkylamine hallucinogens, such as 2,5-dimethoxy-4-iodoamphetamine (DOI).¹⁰ Both indole and phenalkylamine hallucinogens bind primarily to 5-HT₁, 5-HT₂, 5-HT₅, and 5-HT₇ receptors.¹¹ The common effects of these hallucinogens may be mediated by agonist actions at 5-HT₂ receptors,¹² since the potency of hallucinogens in humans correlates well with 5-HT₂ receptor binding affinity in animals,¹³ and the behavioral¹⁴ and electrophysiological¹⁵ effects of hallucinogens in animals can be blocked by 5-HT₂ antagonists. Although these animal data suggest a contribution of the 5-HT₂ receptor system in hallucinogenic drug action, there are, however, some difficulties with interpreting the mechanism of action of these drugs. First, data from animal studies are difficult

to extrapolate to humans, so animal models of hallucinogenic drug action may not reliably predict hallucinogenic properties in humans. Second, LSD has also been reported to stimulate dopamine receptors, suggesting a possible involvement of dopamine in LSD psychosis.¹⁶ Third, psilocybin, although it displays no activity at dopamine receptors,¹⁶ might well modulate the dopamine systems through interactions of central serotonin and dopamine systems.¹⁰ Thus, it remains unclear whether psilocybin and LSD mediate their psychological effects in humans via 5-HT₂ receptor stimulation alone or a subsequent activation of the dopamine systems, or both. Given the suggested importance of 5-HT₂ receptors in schizophrenia and mechanism of action in antipsychotics, it is important to further investigate the role of 5-HT₂ receptors in psychotic symptom formation.

To test the hypotheses that 5-HT₂ and/or DA D₂ receptors contribute to psychological effects of indoleamine hallucinogens in humans, we studied the influence of pretreatment with the 5-HT₂ antagonist ketanserin,¹⁷ the D₂ antagonist and typical antipsychotic haloperidol,¹⁸ or the mixed 5-HT₂/D₂ antagonist and atypical antipsychotic risperidone¹⁸ on the psychotomimetic effects of psilocybin in normal subjects, using a placebo-controlled, within-subject design. The Altered State of Consciousness rating scale (APZ-OAV) was used to assess the psilocybin-induced clinical syndrome because it validly measures changes from the normal waking state independently of the etiology of those changes.¹⁹ In addition, based on our previous metabolic findings in psilocybin subjects,³ we have hypothesized that psilocybin may lead to working memory deficits as seen in schizophrenic patients.²⁰ A visual-manual delayed response task (DRT) was used to measure possible drug-induced alterations in reaction times indicative of spatial working memory deficits.²⁰

Materials and Methods

The study was approved by the Ethics Committee of the Psychiatric University Hospital Zürich and the use of psilocybin by the Swiss Federal Health Office (BAG), Department of Pharmacology and Narcotics (DPN), Bern. Psilocybin was obtained from the BAG (DPN), Bern, and prepared as capsules (1 and 5 mg) at the Pharmaceutical Institute of the University of Bern, Switzerland.

Twenty-five healthy volunteers were recruited from university staff and screened by psychiatric interview to assure that they had neither personal nor family histories of major psychiatric disorders in first-degree relatives. Subjects with a history of illicit drug abuse were excluded from the study. Subjects were healthy according to physical examination,

electrocardiogram, and blood analyses. All subjects gave written informed consent. The psilocybin dose used was high enough (0.25 mg/kg, p.o.) to induce robust psychological alterations over a period of 120–180 min.³ The doses of haloperidol (0.021 mg/kg, i.v.) and risperidone (1 mg, p.o.) chosen were expected to occupy about 55–65% of dopamine D₂ receptors.^{21,22}

Experiment 1: Fifteen subjects (eight male, seven female; mean age ($\pm$ s.d.) 29.7 ± 5.3) were divided into three groups of five and tested at monthly intervals. Subjects in the ketanserin pretreatment experiment received pretreatment with either placebo, 20 mg ketanserin, or 40 mg ketanserin (p.o.); subjects in the haloperidol pretreatment experiment received either placebo, or 0.021 mg haloperidol (i.v.). 75 min later. Subjects of both groups received treatment with either placebo or 0.25 mg/kg psilocybin (p.o.). Subjects in the risperidone pretreatment experiment received pretreatment with either placebo, 0.5 mg risperidone, or 1.0 mg risperidone (p.o.). In these subjects, placebo or 0.25 mg/kg psilocybin (p.o.) was administered 90 min after pretreatment, due to kinetic reasons of risperidone. The (APZ-OAV) rating scale and a delayed response task (DRT) were applied just prior to treatment with either placebo or psilocybin and again 80 min after to coincidence with the peak effects of psilocybin.⁹

Experiment 2: A second group (five male, five female; age 28.4 ± 4.0) received pretreatment with either placebo or 40 mg ketanserin (p.o.). After 75 min subjects received treatment with either placebo or 0.25 mg/kg psilocybin (p.o.). APZ-OAV ratings (but no DRT) were performed according to the protocol of experiment 1.

The Altered State of Consciousness (APZ-OAV) rating scale yields three dimensions (factors) comprised of several item clusters.¹⁹ The first subscale, OSE (oceanic boundlessness), measures derealization and depersonalization phenomena associated with a positive basic mood ranging from heightened feelings to sublime happiness, grandiosity, and alterations in the sense of time and space. The second subscale, VUS (visionary restructuring), assesses illusions, (pseudo-) hallucinations, synaesthetic phenomena, and changes in the meaning of various percepts. The third subscale AIA (dread of ego-dissolution), measures thought disorder, anxious ego-disintegration, loss of control over body and thought, and derealization phenomena associated with arousal and anxiety.

To assess working memory deficits, a visual-manual delayed response task (DRT) was used, as previously reported in detail by Park *et al.*²⁰ and

summarized here. In this DRT, subjects were required to respond to visually presented targets (black circles) by touching a position on a computer screen (a touch screen) with their hand. While subjects sat still on an armchair and stared fixedly at the center of the screen, a target appeared on the screen for 200 ms in one of eight possible locations on the circumference of an imaginary circle. After the presentation of each target, there was a 10 s delay period during which the subject had to perform a category shift task by reading changing numbers appearing in the center of the screen. After that the fixation point and eight reference circles (empty instead of black) appeared on the screen and subjects were required to touch the screen at the remembered position. If the correct target position was hit, the screen cleared and the next trial could begin. If the target position was incorrect, the reference circles remained on the screen until the subjects found the correct position or until 10 s had elapsed, whichever was sooner. There were 32 randomized trials, four at each location. Response times in milliseconds of correct trials were recorded.

The data for each APZ-OAV scale and data for performance on the DRT (response times) were analyzed separately for each antagonist with a two-way ANOVA (analysis of variance) with pretreatment (placebo and dose of antagonist) and drug (placebo and psilocybin) as within-subjects factors. When significant main effects or interactions were revealed in the ANOVA, Tukey *post hoc* comparisons were done. The significance level of the main factors and/or interactions are cited in the text, and those for Tukey's *post hoc* tests of individual groups are shown in the figures. Since haloperidol appeared to increase the psilocybin-induced AIA scores and the reaction time on the DRT, but no significant interactions were found in the two-way ANOVAs, the significance of these increases was also tested using non-parametric Friedman ANOVA. The Spearman correlation coefficient was used to evaluate correlations between changes in reaction time of DRT task and psycho(patho)logical alterations. The criterion for significance was set at $p < 0.05$.

Results

Psilocybin (0.25 mg/kg, p.o.) produced a psychotic syndrome including changes in mood, disturbances of sensory perception and thought processes, and impaired ego-functioning. The drug effects began 20–30 min after administration, peaked after another 30–50 min, and lasted 1–2 h. Thus psychological measurements and neuropsychological testing were undertaken during the peak drug effects.

The APZ-OAV scores for placebo, psilocybin, and psilocybin plus the different doses of antagonists for experiment 1 are summarized in Fig. 1. Two-way ANOVA's and Tukey's *post hoc* comparisons revealed that psilocybin significantly increased the OSE, VUS and AIA scores in the ketanserin, risperidone and haloperidol groups (Fig. 1). The increase in the OSE score was due to a prominent increase in derealization associated with euphoria, exaltation or grandiosity, and an altered sense of time and space. The increase in the VUS score was attributable to perceptual alterations including visual disturbances ranging from illusions to complex scenery hallucinations, synaesthesias, and changed meaning of percepts. The increase in AIA scores was mainly due to an anxiously experienced loss of ego-boundaries, thought disorder, and moderate suspiciousness and paranoid ideation.

As shown in Fig. 1, pretreatment with the 5-HT₂ antagonist ketanserin dose-dependently blocked psilocybin-induced psychosis, as revealed by two-way ANOVAs and significant drug $\times$ pretreatment interactions (OSE ($F(2,8) = 12.2$, $p < 0.004$); VUS ($F(2,8) = 26.3$, $p < 0.0003$); AIA ($F(2,8) = 21.7$, $p < 0.0006$)). Specifically, 20 mg ketanserin reduced the psilocybin-induced APZ-OAV scores by about 50–70%, while 40 mg ketanserin completely prevented the development of psilocybin effects in four of five subjects (98–100%). In the remaining subject, the mean APZ-OAV scores were also markedly reduced (75–87%), but the subject still reported discrete distortions in the experience of time and space, and impaired body control. Similarly, 0.5 mg of the mixed 5-HT₂/D₂ antagonist risperidone attenuated the effects of psilocybin on all three APZ-OAV scales (69–78%), while 1 mg risperidone effectively blocked the development of psilocybin-induced psychosis (98–99%). Two-way ANOVAs yielded again significant drug $\times$ pretreatment interactions (OSE ($F(2,8) = 7.4$, $p < 0.02$); VUS ($F(2,8) = 8.2$, $p < 0.01$); AIA ($F(2,8) = 8.5$, $p < 0.01$)). By themselves, neither ketanserin nor risperidone (0.5 and 1.0 mg) had any effects on any APZ-OAV scores.

In contrast, pretreatment with haloperidol (0.021 mg/kg, i.v.) reduced the effect of psilocybin only on the OSE scale (54% reduction; drug $\times$ pretreatment interaction for OSE ($F(1,4) = 20.4$, $p < 0.01$). Tukey's *post hoc* analysis revealed that this reduction was significant (Fig. 1). Haloperidol had no influence on psilocybin-induced visual illusions and hallucinations as measured by the VUS scale (main effect of drug ($F(1,4) = 52.3$, $p < 0.002$)) and pretreatment ($F(1,4) = 0.51$, $p < 0.5$), and drug $\times$ pretreatment interaction ($F(1,4) = 0.4$, $p < 0.5$)). Surprisingly, haloperidol uniformly increased the AIA scores in all of the subjects treated with psilocybin (148% increase). A

two-way ANOVA revealed significant main effect of drug ($F(1,4) = 14.4$, $p < 0.02$) and pretreatment ($F(1,4) = 8.7$, $p < 0.04$), but no significant drug $\times$ pretreatment interaction ($F(1,4) = 2.1$, $p < 0.22$). Additional non-parametric Friedman ANOVAs showed that this psilocybin-induced increase in AIA scores after haloperidol was significantly greater than psilocybin

alone ($p < 0.025$) and that haloperidol by itself slightly (9.6%), but not significantly, increased the AIA scores as compared to placebo. Furthermore, item-based analysis of the AIA scores revealed that psilocybin mainly increased thought disorder and anxiety after pretreatment with haloperidol.

As seen in Figure 2, psilocybin also increased the reaction time on the memory-guided delayed response task during the peak effects of the drug. Again, ketanserin and risperidone, but not haloperidol, dose-dependently blocked the increase in reaction time on the DRT, as revealed by significant drug $\times$ pretreatment interactions (ketanserin ($F(2.8) = 6.0$, $p < 0.03$); risperidone ($F(2.8) = 4.8$, $p < 0.04$)). Additional Friedman ANOVAs showed that ketanserin, risperidone and haloperidol by themselves did not have any significant effects on reaction times. Performance as measured by the rate of correct responses did not differ significantly between the various conditions. Interestingly, the impairment in reaction time did not correlate significantly with changes in the APZ-OAV scores.

Given the importance of the ketanserin findings obtained in experiment 1, a second group of 10 subjects was tested to corroborate the results obtained with 40 mg ketanserin. Once again, pretreatment with 40 mg ketanserin effectively blocked the effects of psilocybin on all APZ-OAV measures by 87–96%. Two-way ANOVAs yielded significant drug $\times$ pretreatment interactions for OSE ($F(1.9) = 51.7$, $p < 0.0001$), VUS ($F(1.9) = 111.7$, $p < 0.00001$), and AIA ($F(1.9) = 16.2$, $p < 0.003$) and Tukey's *post hoc* comparisons confirmed that these effects were significant (Fig. 3).

Discussion

The present results provide compelling evidence that the model psychosis induced by psilocybin in healthy human volunteers is the result of a specific activation of the 5-HT₂ subtype of serotonin receptors. These findings validate the many studies in animals indicating that the behavioral effects of hallucinogens are attributable to 5-HT₂ agonist actions.

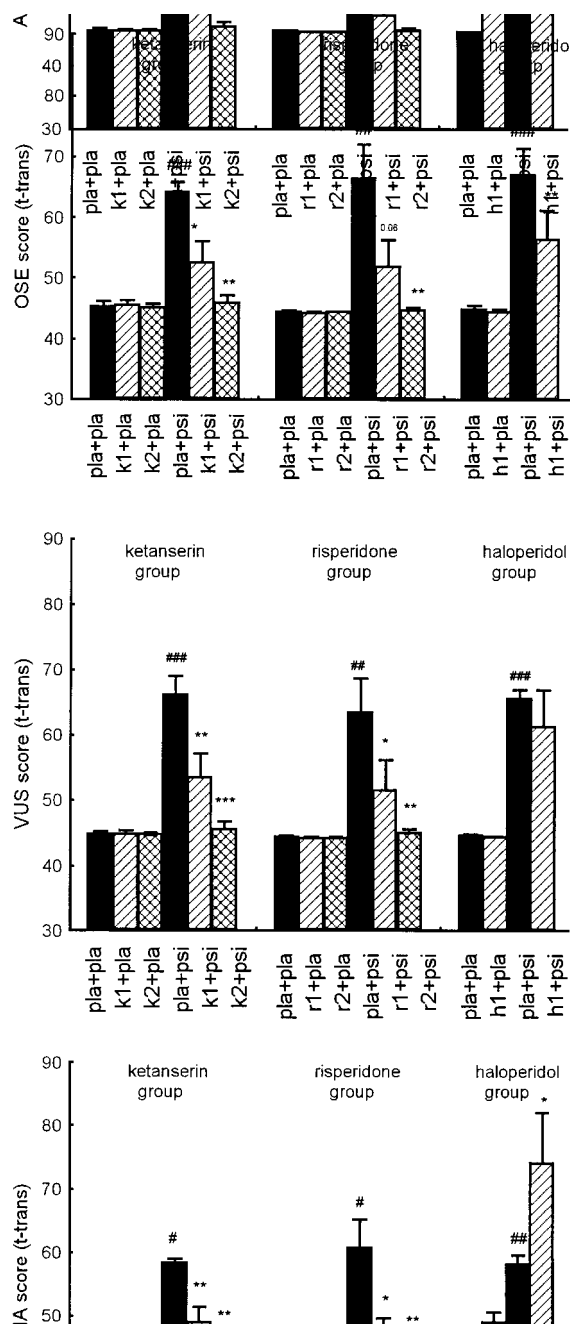


FIG. 1. Bars show the pretreatment alone effects of placebo, ketanserin, risperidone and haloperidol, and the effects of pretreatment on the psilocybin-induced APZ-OAV scores (OSE, VUS and AIA) in normal subjects. The OSE scale includes items for derealization and depersonalization associated with euphoria, the VUS scale rates illusions, hallucinations, and changed meaning, and the AIA scale rates anxious ego-dissolution, thought disorder, and paranoia. Data are means $\pm$ s.e. ($n = 5$ for each antagonist): placebo (pla), psilocybin (psi = 0.25 mg/kg), ketanserin (k1 = 20 mg, k2 = 40 mg, p.o.), risperidone (r1 = 0.5 mg, r2 = 1.0 mg, p.o.) and haloperidol (h1 = 0.021 mg/kg, i.v.). Significant increases from placebo to psilocybin: # $p < 0.05$, ## $p < 0.01$, ### $p < 0.001$. Significant decreases from psilocybin to antagonist conditions: * $p < 0.05$, ** $p < 0.01$ (Tukey's *post hoc* test). Note: The psilocybin-induced increase in AIA after haloperidol was tested by a Friedman ANOVA.

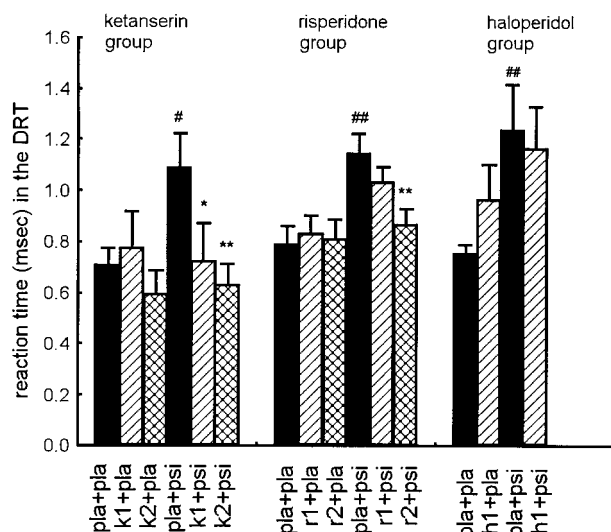


FIG. 2. Bars show the pretreatment alone effects of placebo, ketanserin, risperidone, and haloperidol and the effects of pretreatment on the psilocybin-induced spatial working memory deficits as measured by a memory-guided delayed response task (DRT). Data are means $\pm$ s.e. ($n = 5$ for each antagonist). For abbreviations see Fig. 1. Significant increases in reaction time (rt) from placebo to psilocybin: # $p < 0.05$, ## $p < 0.01$. Significant decreases from psilocybin to antagonist conditions: * $p < 0.05$, ** $p < 0.01$ (Tukey's *post hoc* test). Note: The psilocybin-induced increase in reaction time after haloperidol was tested by a Friedman ANOVA.

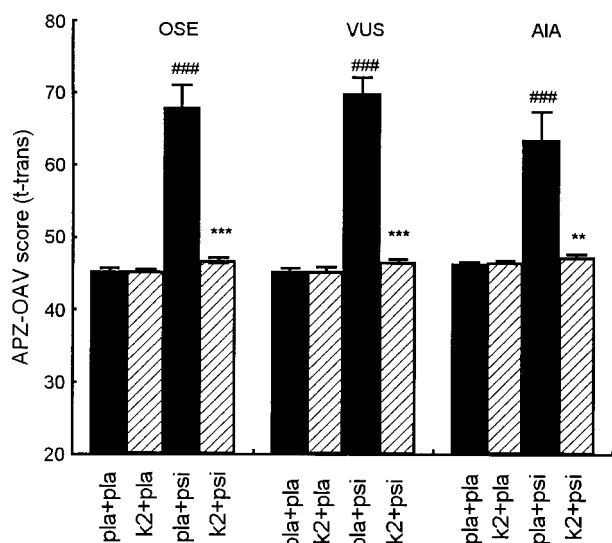


FIG. 3. A second experiment to corroborate the effects of placebo and ketanserin pretreatment on the psilocybin-induced APZ-OAV scores was performed in normal subjects. Data are means $\pm$ s.e. ($n = 10$): placebo (pla), ketanserin (k2 = 40 mg, p.o.) and psilocybin (psi = 0.25 mg/kg). Significant increases from placebo to psilocybin: ### $p < 0.001$. Significant decreases from psilocybin to antagonist conditions: ** $p < 0.01$, *** $p < 0.001$ (Tukey's *post hoc* test).

This study corroborates the several previous suggestions of similarities between the early and acute stages of schizophrenia and the psychological effects of indoleamine-derived hallucinogens such as psilocybin and LSD.^{3,5,7} In particular, the finding that psilocybin produced derealization and

depersonalization associated with heightened mood, euphoria and/or grandiosity (OSE) and visual hallucinations (VUS) is consistent with the observation that the earliest affective changes in incipient schizophrenia are often pleasurable and that visual, as opposed to auditory, hallucinations occur with higher prevalence in first-break than chronic schizophrenics.⁷ Anxious ego-dissolution, loss of body and thought control, and ideas of reference (AIA), however, are not only common features of both psilocybin-induced psychosis and early schizophrenic stages, but also occur in chronic schizophrenics in acute episodes. Indeed, a recent study demonstrated that schizophrenics during both first episodes and relapse had similar prominent OSE and AIA scores as seen in this study in psilocybin subjects.¹ The most novel aspect of the present findings is the demonstration that psilocybin-induced psychosis could be completely prevented by either the atypical neuroleptic and mixed 5-HT₂/D₂ antagonist risperidone or by the 5-HT₂ antagonist ketanserin, but not by the typical neuroleptic and D₂ antagonist haloperidol. This finding adds substantial evidence to the view that 5-HT₂ agonism is responsible for the psychological effects of psilocybin and, presumably, other indoleamine hallucinogens. Furthermore, the finding that ketanserin, with about 100-fold greater potency at the 5-HT_{2A} vs 5-HT_{2C} receptor, completely blocked psilocybin-induced psychosis strongly indicates that the effects of psilocybin are mediated by 5-HT_{2A} rather than 5-HT_{2C} receptor activation. This interpretation is corroborated by recent findings demonstrating that the highly selective 5-HT_{2A} receptor antagonist M100,907 (formerly MDL 100,907), but not 5-HT_{2C} antagonists, completely antagonized the disruptive effect of the hallucinogenic 5-HT_{2A/C} agonist DOI on prepulse inhibition (PPI) of startle in rats.¹⁴ Insofar that PPI deficits and 5-HT_{2A} receptor alterations were recently found in schizophrenic patients,²³ the present data are consistent with the hypothesis that serotonergic hyperactivity may also contribute to the pathophysiology of schizophrenia.

To the extent that the effects of psilocybin studied here are relevant to the symptoms of acute schizophrenia, the blockade of these effects by a 5-HT₂ antagonist supports the notion that 5-HT₂ antagonism may contribute significantly to the antipsychotic actions of atypical neuroleptics.¹⁸ In this regard, it is particularly interesting to note that the typical antipsychotic haloperidol was substantially less effective than risperidone in blocking the psychosis-like symptoms produced by psilocybin, despite the fact that the doses of haloperidol and risperidone were selected to have comparable effects on dopamine D₂ receptors.^{21,22} In contrast,

haloperidol even increased psilocybin-induced AIA scores. This finding might be somewhat surprising, but is consistent with single case reports indicating that classic neuroleptics do enhance, rather than ameliorate, LSD-induced psychosis.²⁴ Whether psilocybin increases the AIA scores after pretreatment with haloperidol through a serotonergic modulation of dopamine or other neurotransmitter systems, such as GABA,¹⁰ or both, cannot be inferred from the present data. Nevertheless, despite the fact that psilocybin and psilocin do not act directly upon D2 receptors¹⁶ haloperidol partially ameliorated psilocybin-induced OSE scores. This finding could indicate that psilocybin has an indirect influence on dopaminergic systems which is then antagonized by haloperidol. Finally, haloperidol, in contrast to ketanserin and risperidone, had no effects on psilocybin-induced perceptual disturbances and hallucinatory phenomena (VUS) indicating that these symptoms are specifically attributable to direct activation of 5-HT_{2A} receptors and do not depend upon the dopaminergic system.

The second important result was that psilocybin produced spatial working memory deficits comparable to those seen in schizophrenic patients²⁰ and that these deficits could be completely prevented by 5-HT₂, but not D2 antagonism. This finding strongly suggests that 5-HT₂, and particularly 5-HT_{2A} receptor stimulation, may also contribute to cognitive impairments in schizophrenia. This interpretation is consistent with the observation that schizophrenic patients with cognitive deficits respond better to atypical than typical neuroleptics.²⁵ Furthermore, the observation that psilocybin-induced working memory deficits did not correlate with psychopathological measures is in line with the notion that cognitive deficits in schizophrenia appear to occur independent of positive and negative symptoms of schizophrenia.²⁵

Conclusion

The present study demonstrated that psilocybin produces schizophrenia-like symptoms primarily through 5-HT₂ receptor stimulation. This finding adds further evidence to the hypothesis that excessive 5-HT₂ receptor activation, particularly 5-HT_{2A},

may be a critical factor in psychotic symptom formation and cognitive deficits in schizophrenia, at least in a subset of schizophrenic patients.²³ Thus, selective 5-HT_{2A} antagonists may be useful in normalizing such imbalances.¹⁸ Furthermore, the classic amphetamine-induced model of psychosis has generally been used to assess the actions of typical antipsychotics, such as haloperidol, whose efficacy appears to be attributable to dopamine antagonism. By contrast, it appears that the psilocybin-induced psychosis may offer a potential model to study specifically those aspects of atypical antipsychotic action that differ from the actions of typical antipsychotics.

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