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Effects of the hallucinogen psilocybin on habituation and prepulse inhibition of the startle reflex in humans

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Schizophrenic patients exhibit deficits in indices of sensorimotor gating, such as habituation and prepulse inhibition (PPI) of the startle reflex. Hallucinogenic drug-induced states are putative models for the early and acute stages of schizophrenic and schizophrenia-spectrum disorders. Hallucinogenic drugs have been shown to disrupt PPI and/or retard habituation of the startle reflex in animal models of schizophrenia, consistent with the view of hallucinogen-induced states as 'model psychoses'. We evaluated the effects of the hallucinogen psilocybin on PPI and habituation of the startle reflex in a double-blind, placebo-controlled human study with 12 healthy subjects. In contrast to animal studies, in our small human sample, psilocybin increased PPI, while having no clear effect on habituation ($n = 6$). These findings must be considered preliminary because several factors, including dose regimens and experimental parameters, may influence the results of studies on startle plasticity. Further investigations both with psychotic patients in different stages of the disease and with human and animal models of schizophrenia are needed in order to explore the effects of hallucinogens on sensorimotor gating and the relationship between information processing in hallucinogenic drug-induced states and the naturally occurring psychoses. Behav Pharmacol 1998; 9:561–566

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INTRODUCTION

Deficits in habituation and prepulse inhibition (PPI) of the startle reflex have been demonstrated repeatedly in schizophrenic patients (Braff *et al.*, 1978, 1992; Geyer and Braff, 1982, 1987; Grillon *et al.*, 1992; Bolino *et al.*, 1994). These abnormalities have been related to hypothetical deficits in inhibitory mechanisms affecting information processing and allowing for filtering and prevention of overload of the organism with irrelevant information (Braff and Geyer, 1990). This hypothetical 'failure to inhibit' could be related to hallmark clinical features of schizophrenic patients, such as intrusive thoughts and sensory experiences, and impaired attentional capacity (Geyer and Braff, 1987; Swerdlow *et al.*, 1992). In more recent studies, impaired PPI in schizophrenic patients was associated with thought disorder (Perry and Braff, 1994), increased semantic priming effects in a lexical decision task (Vinogradov *et al.*, 1996), high distractability on a continuous performance test (Karper *et al.*, 1996), and lateralized attention deficits on a covert orienting of attention task (Karper *et al.*, 1996). Furthermore, deficits in latent inhibition and negative priming were frequently demonstrated in schizophrenic patients, and are thought to reflect similar failures in inhibitory pathways of information processing as PPI deficits (McDowd *et al.*, 1993; Hemsley, 1993; Gray *et al.*, 1995; Lubow and Gerwirtz, 1995). The majority of studies have been performed with clinically stable patients, who were mostly on neuroleptic medications. However, there is some preliminary evidence that latent inhibition is disrupted in acute, but not in chronic schizophrenic patients (Gray *et al.*, 1995), and that PPI deficits in schizophrenic patients may be restored by successful neuroleptic treatment (Wu *et al.*, 1992; Hamm *et al.*, 1995; Weike *et al.*, 1996). In view of these results, and taking into account clinical experience and intuition, one might hypothesize that deficits in PPI and habituation may be more severe during acute, productive episodes of the disorder.

Hallucinogenic drug-induced states may be employed as models for the acute episodes of schizophrenic and schizophrenia spectrum psychoses. Such 'model psychoses' may provide useful research tools for explorations into biological mechanisms related to the naturally occurring psychoses (Hermle *et al.*, 1992; Spitzer *et al.*, 1996; Vollenweider *et al.*, 1997a, b; Gouzoulis-Mayfrank *et al.*, 1998a). Animal models of schizophrenia also employ hallucinogenic drugs along with high dose psychostimulant drugs (Geyer and Markou, 1995). Several classic hallucinogens, such as lysergic acid diethylamide (LSD), mescaline and 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI), psychotomimetic *N*-methyl-D-aspartate (NMDA) antagonists, such as phencyclidine, ketamine and dizocilpine, and entactogens (ecstasy), such as 3,4-methylenedioxymethamphetamine (MDMA), 3,4-methylenedioxyethamphetamine (MDE) and alpha-ethyltryptamine were shown to impair habituation and/or disrupt PPI of the startle reflex in laboratory animals (reviewed by Geyer, 1998). Recent data from animal studies demonstrating disruption of latent inhibition by ketamine and DOI (Hitchcock *et al.*, 1997; Gallo *et al.*, 1998) and enhancement of latent inhibiton by typical and atypical antipsychotic drugs (Weiner *et al.*, 1996; Williams *et al.*, 1997; Trimble *et al.*, 1997) are in line with the findings from the above mentioned PPI studies. Evidence from a large body of pharmacological studies employing agonists and antagonists corroborates the importance of central serotonergic systems for the effects of hallucinogens and entactogens on measures of startle plasticity. In addition, atypical antipsychotics with antiserotonergic properties, such as clozapine and olanzapine, have been shown to reverse the PPI-disrupting effects of NMDA antagonists in laboratory animals (reviewed in Geyer, 1998). In a recent study, the psychotomimetic NMDA-antagonist ketamine attenuated PPI in human subjects (Karper *et al.*, 1995). In light of these results, we hypothesized that classic hallucinogenic drugs should also disrupt PPI in humans.

To test this hypothesis, we conducted a double-blind study with healthy human subjects, who received either the hallucinogen psilocybin or placebo. This investigation was part of a more comprehensive project with 32 volunteers and four substances (the hallucinogen psilocybin, the entactogen MDE, the stimulant *d*-methamphetamine, and placebo: $n = 8$ in each group). The study was designed to compare the effects of these different drugs on multiple measures including psychopathology, neurometabolism, neuropsychological performance and plasticity of the startle reflex. Methodological problems of the startle study included non-responsiveness in some subjects, many artifacts due to bruxism in the MDE group, and different dose regimens due to different sensitivity of the subjects to stimulant effects in the *d*-methamphetamine group. These difficulties resulted in many missing values and very small sizes of the remaining groups, particularly of the MDE and *d*-methamphetamine groups. Consequently, meaningful statistical analyses were impossible for the MDE and *d*-methamphetamine groups. Therefore, in this paper we report only on the data of the psilocybin and placebo groups.

METHODS

The study was carried out in accordance with the Declaration of Helsinki and was approved by the local ethics committee at the Medical Faculty of the Institute of Technology (RWTH) and the Federal Health Administration (BGA, Bundesopiumstelle, Berlin).

Subjects

Sixteen healthy volunteers (nine men, seven women; mean age, 32.9 years; range, 27–45 years) with no current or previous history of significant physical, neurological or psychiatric disorder [Axis I and II according to Diagnostic Statistical Manual (DSM-III-R) criteria], no family history of severe psychiatric disorder in first degree relatives, and no regular medication were included in the study. All subjects were either physicians ($n = 11$) or psychologists ($n = 5$). Each volunteer gave written informed consent. Before entering the study, subjects were screened by means of a medical history, clinical examination including a clinical test for normal hearing, electrocardiogram (ECG), routine laboratory testing, as well as a standardized psychiatric interview (SCID) supplemented by a clinical interview that further evaluated personal and family history. Subjects were not screened for startle responsiveness before entering the study. After exclusions for non-responsiveness or severe artifacts, six subjects remained in each group (psilocybin: two men, four women; mean age, 32.3 years; range, 29–36 years; placebo: four men, two women; mean age, 33.8 years; range, 27–40 years).

Drugs

All substances were obtained from the Pharmaceutical Institute, University of Tübingen, Germany, and were prepared as capsules of identical appear-

ance. The calculated individual psilocybin dose (approximately 0.2 mg/kg, but not more than 15 mg total dose) was made available by combination of 2.5-mg and 10-mg capsules. Empty placebo capsules were added, so that all volunteers received a total of five capsules, which they ingested with water.

Each subject participated in two experiments with the same substance (psilocybin or placebo) in a double-blind design and pseudo-randomized order. Acccording to the overall design of the study, subjects knew that they might receive either placebo, psilocybin, MDE, or *d*-methamphetamine. As expected, all psilocybin subjects displayed significant psychological effects including perceptional distortions, alterations of mood and drive, formal thought disorders and attentional deficits. Typical psychotic symptoms, such as ideas of reference, transient paranoid thoughts and visual, as well as auditory, hallucinations were observed in two cases (Gouzoulis-Mayfrank *et al.*, 1998b). All psilocybin subjects guessed correctly that the drug they had received was the hallucinogen psilocybin. Subjects on placebo experienced either no or minor psychological effects including relaxation and peacefulness in one case, and mild activation and heightened colour perception in another. Accordingly, these two subjects thought that they might have received MDE, or *d*-methamphetamine, respectively, although they both considered the possibility of placebo effects. The remaining four placebo subjects guessed correctly that they had received placebo.

Procedure

The startle study was performed on the second experimental day. Experiments were performed in a quiet laboratory room in the Department of Psychiatry. Fasting subjects arrived at the hospital between 08:00 and 09:00 h. A startle session was performed about 1 h prior to ingestion of the drug. Drugs were administered between 10:00 and 11:00 h, and thereafter subjects were allowed to relax. An experienced psychiatrist accompanied the subjects for the entire duration of the experiment. After the psychological symptoms emerged and became prominent (about 75–90 min after drug ingestion), the same startle session was repeated. In the cases where no apparent psychological changes occurred, the startle session began 90 min after drug ingestion. Subjects remained in the Psychiatric Department for at least 2 h after complete resolution of the psychological effects (typically 6–8 h after drug ingestion).

Electromyographic activity (EMG) of the orbicularis oculi muscle was recorded with a commercially available startle system (SR-Lab; San Diego Instruments, San Diego, CA, USA) using two disc electrodes placed below the right eye. Startle responses were assessed by examining the amplitude of eyeblink responses (in digital units) to acoustic stimuli, which were delivered binaurally through headphones (TDH-39-P, Maico, Minneapolis, MN, USA). The procedures and criteria for startle responses employed in this study were identical to those used previously (Braff *et al.*, 1992). During both sessions (pre-drug and on-drug), subjects were seated comfortably in a bed with head and upper trunk supported and were instructed to fixate a blank space on the opposite wall. The session consisted of three blocks including five, 31 and five trials, respectively (total, 41 trials). Ten different intertrial intervals (range, 8–22 s) were used randomly. The first trial was given following an acclimation period of 5 min to the background of 70-dB white noise. The first and the third block consisted of five pulse alone trials with a stimulus intensity of 115 dB. The second block consisted of 10 PA trials and 21 prepulse trials with three different prepulse intensities (4, 8 and 16 dB over background noise; seven trials each), which were presented in a pseudo-randomized order. The duration of both prepulses and pulses was 20 ms, and the prepulse-to-pulse interval was 100 ms.

Habituation and prepulse inhibition (PPI) were calculated as percentage scores. Habituation was defined as the difference in mean magnitude between the first and third block, divided by the corresponding value of the first block, multiplied by 100. PPI was defined as the difference in mean magnitude between pulse alone and prepulse trials of the second block, divided by the corresponding pulse alone value, and multiplied by 100. Differences between pre-drug and on-drug sessions were analysed separately for the placebo and psilocybin groups by means of Wilcoxon tests for matched-pair comparisons. The arithmetic differences between pre-drug and on-drug values of both drug groups were analysed by means of Mann–Whitney U-tests. Although data are presented as means and standard errors, non-parametric inferential tests were used because of the small sample sizes.

RESULTS

The placebo and psilocybin groups did not differ significantly in the overall startle responsiveness. The mean amplitudes of the blink reflex [in digital units ± standard deviation (SD)] in the first block of both sessions were: pre-drug session: placebo: 124.8 ± 21.8; psilocybin: 180.57 ± 78.0; on-drug session: placebo: 110.2 ± 31.9; psilocybin: 117.7 ± 59.0 (Mann–Whitney U-tests, $P > 0.05$). There were no

effects of psilocybin on response onset and peak latency. Therefore, these data are not shown.

Mean values and deviation of habituation and prepulse inhibition (PPI) of the two sessions (pre-drug and on-drug) are presented in Table 1 and Figure 1 ($n = 6$ in both groups; missing values were due to startle non-responsiveness and/or artifacts). In the placebo group, habituation and PPI remained stable across the two sessions. In the psilocybin group, PPI was higher in the pre-drug compared to the on-drug session at the two higher prepulse intensities. The increase of 8-dB PPI was significant at the 5% level ($P = 0.05$, Wilcoxon test), while the increase of 16-dB PPI approached statistical significance ($P = 0.075$, Wilcoxon test).

In addition, mean values and standard deviation of the arithmetic differences in habituation and PPI between on-drug and pre-drug sessions (on-drug – pre-drug) were calculated. The difference in 8-dB PPI between the placebo and psilocybin groups was significant at the 5% level (placebo: −2.81 ± 20.94, psilocybin: 15.19 ± 10.45, $P < 0.05$, Mann–Whitney U-test), whereas the difference in 16-dB PPI approached significance (placebo: −0.49 ± 10.41, psilocybin: 12.92 ± 15.05, $P = 0.109$, Mann–Whitney U-test).

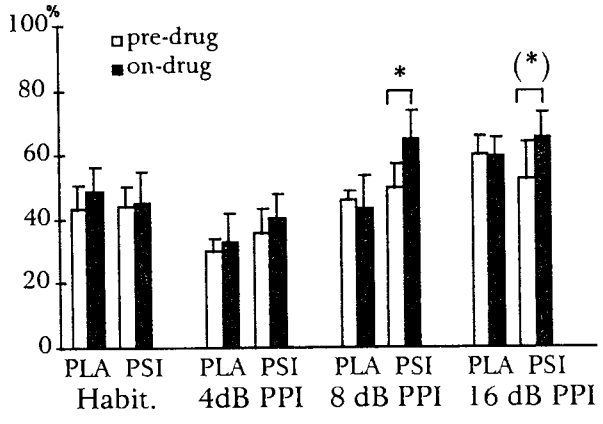

FIGURE 1. Habituation and prepulse inhibition (PPI) of the startle reflex in precentage (mean values and standard error) under psilocybin (PSI) and placebo (PLA) before and after drug administration (n = 6 in each group) (*P < 0.05; (*)P < 0.1, Wilcoxon test).

DISCUSSION

Based on the results of previous studies both with schizophrenic patients and laboratory animals under hallucinogenic drugs, we hypothesized that the hallucinogen psilocybin should disrupt prepulse inhibition (PPI) and/or retard habituation of the startle reflex in healthy human subjects. In this study of a small sample of healthy volunteers, we were not able to demonstrate the expected effects. Rather, psilocybin increased PPI with the 8-dB prepulse intensity and tended to increase it with the highest prepulse intensity of 16-dB.

From a clinical point of view, the theory that sensorimotor gating or filtering deficits may contribute to sensory overload and cognitive disorganization in psychotic patients is understandable (Braff and Geyer, 1990; Braff *et al.*, 1992). Within this theoretical framework, our findings would suggest that subjects under psilocybin are able to inhibit or filter irrelevant information very effectively. Considering the psychopathological effects of hallucinogens and the use of the psilocybin state as a 'model psychosis' (Vollenweider *et al.*, 1997b; Gouzoulis-Mayfrank *et al.*, 1998), this interpretation appears strongly contra-intuitive and puzzling. Drug dosage is the first factor that may strongly influence the results of studies on startle plasticity. The hallucinogen doses used in animal studies are much higher than the doses administered in investigations with human subjects (reviewed in Geyer, 1998). In our study, we used a moderate dose that was sufficient to induce significant, but not maximal, psychotomimetic effects, in order for the subjects to be able to co-operate in task procedures. Consequently, all subjects experienced perceptional alterations, cognitive disturbances and mood shifts, but few subjects experienced full-

TABLE 1. Mean values (in percentage) ± standard deviation of habituation and prepulse inhibition (PPI) in the psilocybin (PSI) and placebo (PLA) group

	PLA			PSI		
	Pre-drug	On-drug	P	Pre-drug	On-drug	P
Habit	43.27±14.62	48.72±17.43	0.398	43.91±12.89	445.24±19.69	0.196
PPI 4 dB	30.26±6.97	33.01±17.56	0.753	35.86±14.32	40.51±14.94	0.916
PPI 8 dB	45.96±6.23	43.15±21.04	0.345	**49.53±15.41**	**64.72±18.33**	**0.046**
PPI 16 dB	59.94±11.59	59.46±11.90	0.463	**52.52±22.68**	**65.44±15.09**	**0.075**

n = 6/group. Significant or trends effects are indicated using bold characters (P, Wilcoxon test).

blown psychotic symptoms, such as hallucinations, paranoid thoughts, temporary impairment of ego-control and loss of insight into the artificial nature of their experiences (Gouzoulis-Mayfrank *et al.*, 1998b). Theoretically, enhanced sensorimotor gating in such a 'pre-psychotic' state might be the expression of a compensatory effort to overcome the imminent flooding of the organism with sensory overload. In the full-blown psychotic state, this compensatory effort might be inadequate, and cognitive fragmentation would result. Accordingly, one might indeed expect to find deficits in PPI and habituation after administration of higher doses of hallucinogenic drugs in humans. However, our limited data do not permit for clear conclusions in respect to this subject and PPI did not appear to be associated with the intensity of psychopathological effects in our sample. In particular, the two subjects displaying the most marked psychosis-like psychopathological alterations did not present reduced PPI or habituation of the startle reflex. Variations in prepulse intensities and prepulse-to-pulse intervals may be additional factors that influence results, since the mechanisms involved in gating and habituation may vary across these parameters. These variations might result in different and even opposite effects on measures of sensorimotor gating and habituation.

Clearly, due to the small sample size of our study, these findings must be regarded as preliminary and should be replicated on a larger scale. Theoretically, given the number of comparisons carried out for pre-drug versus on-drug effects, the emergence of single significant findings may be due to chance. Nevertheless, it is interesting that two very recent studies of other groups also reported increases in PPI in healthy humans after administration of drugs that disrupt PPI in animals, specifically the entactogen MDMA (Vollenweider *et al.*, 1997c) and the dissociative anaesthetic ketamine (Duncan *et al.*, 1997). Moreover, the few MDE and *d*-methamphetamine data of our study also reveal a tendency towards increased PPI after intake of these drugs. Taken together, these findings suggest that further investigations with different drugs, dose regimens and parameters (pulse and prepulse intensities, intervals and sensory modalities) are needed in order to elucidate the effects of hallucinogenic and related drugs on measures of gating and information processing. Inclusion of related cognitive measures, such as latent inhibition and negative priming, which are also thought to reflect inhibitory mechanisms of information processing, could be helpful in future PPI studies with psychotropic drugs . Moreover, longitudinal studies with endogenously psychotic patients in different stages of the disorder would be highly desirable. Taken together, these studies could shed more light on the suggested relationship between information processing in hallucinogenic drug-induced states and the naturally occurring psychoses.

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