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ORIGINAL INVESTIGATION

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Acute psychological and physiological effects of psilocybin in healthy humans: a double-blind, placebo-controlled dose–effect study

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Abstract *Rationale:* Serotonin (5-Hydroxytryptamine, 5-HT) receptors play an important role in perception, affect regulation and attention. Pharmacological challenge with the 5-HT_{2A} agonist psilocybin (PY) is useful in studying the neurobiological basis of cognition and consciousness. *Objective:* Investigation of dose-dependent effects of PY on psycho(patho)logical and physiological parameters. *Methods:* Eight subjects received placebo (PL), and 45 ("very low dose, VLD"), 115 ("low dose, LD"), 215 ("medium dose, MD"), and 315 ("high dose, HD") μg/kg body weight PY. The "Altered States of Consciousness Rating Scale" (5D-ASC), the "Frankfurt Attention Inventory" (FAIR), and the "Adjective Mood Rating Scale" (AMRS) were used to assess the effects of PY on psycho(patho)logical core dimensions, attention, and mood. A 24-h electrocardiogram (EKG) was recorded and blood pressure was measured. Plasma concentrations of thyroid-stimulating hormone (TSH), prolactin (PRL), cortisol (CORT), adrenocorticotropic hormone (ACTH), and standard clinical chemical parameters were determined. *Results:* PY dose dependently increased scores of all 5D-ASC core dimensions. Only one subject reacted with transient anxiety to HD PY. Compared with PL, MD and HD PY led to a 50% reduction of performance in the FAIR test. "General inactivation", "emotional excitability", and "dreaminess" were the only domains of the AMRS showing increased scores following MD and HD PY. The mean arterial blood pressure (MAP) was moderately elevated only 60 min following administration of HD PY. Neither EKG nor body temperature was affected by any dose of PY. TSH, ACTH, and CORT plasma levels were elevated during peak effects of HD PY, whereas PRL plasma levels were increased following MD and HD PY. *Conclusion:* PY affects core dimensions of altered states of consciousness and physiological parameters in a dose-dependent manner. Our study provided no cause for concern that PY is hazardous with respect to somatic health.

Keywords Psilocybin · Dose–effect study · Psycho(patho)logy · Neuroendocrinology · Cardiovascular effects · Altered states of consciousness

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Introduction

The indolealkylamine psilocybin (PY, 4-phosphoryloxy-*N,N*-dimethyltryptamine) is the main psychoactive principle of hallucinogenic mushrooms such as *Psilocybe cubensis* and *Psilocybe semilanceata*. PY interacts mainly with serotonergic neurotransmission (5-HT_{1A}, 5-HT_{2A}, and 5-HT_{2C} receptor subtypes). Equilibrium dissociation constants (K_i) are 6 nM for the 5-HT_{2A} receptor subtype and 190 nM for the 5-HT_{1A} subpopulation (McKenna et al. 1990). PY and its active metabolite psilocin (PI) have—in contrast to lysergic acid diethylamide (LSD)—no affinity for dopamine D2 receptors (Creese 1975). In a receptor-blocking study, we showed that the psychotropic effects of PY could be blocked completely by pretreatment with the 5-HT_{2A} preferential antagonist ketanserin (Vollenweider et al. 1998) suggesting that PY-induced effects are mediated primarily via activation of 5-HT_{2A} receptor subtypes. However, some of the psychotropic effects of PY might be due to downstream effects on other neurotransmitter systems. For example, we recently demonstrated in a PET study using the D2-receptor ligand [^{11}C] raclopride that PY increases striatal dopamine (Vollenweider et al. 1999). The enhanced dopaminergic activity correlated with derealization/depersonalisation phenomena and euphoria. Corresponding functional interactions of central dopaminergic and serotonergic systems have been demonstrated (Kapur and Remington 1996). The pharmacology of PY is reviewed in a paper by Passie et al. (2002). Aside from the popular (illicit) use as a recreational drug (Cuomo et al. 1994; Lohrer and Albers 1999; Supprian et al. 2001), PY can

serve as an experimental tool in neurosciences to study the neurobiological basis of altered states of consciousness (ASC) (Vollenweider et al. 1997; Gouzoulis-Mayfrank et al. 1998; Vollenweider et al. 1999; Vollenweider and Geyer 2001). Recent investigations revealed that the serotonin (5-HT) receptor system is of basic importance also in the modulation of cognitive functions such as memory and attention (Meneses 1998; Buhot et al. 2000; Ellis and Nathan 2001). Depending on the context, activation or inhibition of 5-HT_{2A} receptors leads to an improvement or an impairment of working memory function (Williams et al. 2002). Hence, the 5-HT_2 receptor agonistic mode of action of psilocin (PI, 4-hydroxy-*N*,*N*,-dimethyltryptamine), the first and pharmacologically active metabolite of PY (Hasler 1997; Lindenblatt et al. 1998) makes this "classic" hallucinogen also an interesting compound to investigate brain mechanisms underlying attention. In view of the diverse and widespread use of PY, its pharmacological and toxicological properties in humans must be closely investigated in order to estimate the safety of PY.

Our literature review revealed two human studies on the acute somatic effects of PY from 1959 and 1961 (Isbell 1959; Hollister 1961) and one study published in 1999 by Gouzoulis-Mayfrank et al. (Gouzoulis-Mayfrank et al. 1999) using a single dose of PY in eight subjects. Isbell found a clinically irrelevant, although statistically significant, elevation of systolic blood pressure after administration of 86 μg/kg body weight PY, but not after 114 μg/kg. Hollister's clinical-chemical measures of serum cholesterol, alkaline phosphatase, cholinesterase, and aspartatamino-transferase revealed no differences between baseline blood samples and samples taken 2 h post-dose. Gouzoulis et al. (Gouzoulis-Mayfrank et al. 1999) found no significant response of cortisol, prolactin, or growth hormone on administration of a single moderate dose of PY (200 μg/kg). In the same trial, weak elevations of systolic blood pressure and body temperature were noted. In a human study by Strassman and Qualls (1994), intravenous *N*,*N*- dimethyltryptamine (DMT), a hallucinogenic compound chemically related to PI, dose dependently raised prolactin and cortisol plasma levels.

The primary aim of this study was to explore the potential dose–response relationship of PY on multiple levels, encompassing various (neuro-)psychological and physiological parameters. The second aim was to estimate the drug safety of PY for further use in human challenge studies and to appraise possible associated risks.

Materials and methods

Subjects

Eight volunteers (four male and four female; mean age 29.5 years, range 22–44 years) were recruited from university and hospital staff by word of mouth and agreed to participate in the study with written informed consent. Subjects were healthy according to physical examination, detailed clinical-chemical blood analysis, and electrocardiogram. All subjects were screened by structured psychiatric interview based on the DIA-X computerized diagnostic expert system (Wittchen and Pfister 1997). Personal and family histories of major psychiatric diseases as well as personal histories of illicit drug use were employed as exclusion criteria. The screening procedure was supplemented by standard psychometric instruments (Freiburg Personality Inventory FPI, Fahrenberg et al. 1984; State Trait Anxiety Inventory, Trait form STAI-X2; Laux et al. 1981; and Hopkins Symptom Checklist SCL-90, Derogatis et al. 1973). Since the personality trait factors "rigidity" and "emotional lability" were identified to be predictors of negative experiences during ASC (Dittrich 1993), scores exceeding two SD from the mean value of normative data in the respective subscales of the FPI (i.e., "openness" and "neuroticism") were used as exclusion criteria. Apart from sporadic use of cannabis, our subjects had no or very limited experience with psychoactive drugs. All subjects were of normal weight (mean body mass index 21.4, range 18.5–23.5) and all female volunteers had a regular menstrual cycle and did not receive oral contraceptives.

Substances

PY for neurochemical stimulation was obtained through the Swiss Federal Office for Public Health, Department of Pharmaceutics and Narcotics, Bern. PY capsules (1 mg and 5 mg) were prepared at the Pharmacy of the Cantonal Hospital of Aarau, Switzerland. Quality control comprised tests for identity, purity and uniformity of content. PY and lactose placebo were administered in gelatin capsules of identical appearance.

Study design

The study protocol was approved by the ethics committee of the University Hospital of Zürich. Administration of PY to healthy subjects was authorized by the Swiss Federal Office for Public Health, Department of Pharmaceutics and Narcotics, Bern. According to our within-subject study design, each volunteer received placebo (PL) and four different doses of PY in random order on five experimental days at least 2 weeks apart. PY dosages were as follows: very low dose (VLD) = 45 μg/kg body weight; low dose (LD) = 115 μg/kg; medium dose (MD) = 215 μg/kg; and high dose (HD) = 315 μg/kg. Our own investigations (Hasler 1997; Hasler et al. 1997) revealed that identical doses of PY relative to body weight cause comparable plasma concentration–time profiles of PI. We therefore preferred to administer doses relative to body weight rather than absolute amounts of PY. Both volunteers and investigators were blind with respect to the experimental condition. To minimize confounding effects of circadian rhythms on hormone levels, drug dosing took place at approximately the same time. In all female volunteers, the experiments were performed during the early follicular phase of their menstrual cycles. Experienced psychiatrists supervised all experiments.

Psychometric scales

Dimensions of ASC

The rating scale 5D-ASC (Dittrich 1998; Dittrich et al. 1999) is a visual-analogue scale suited to depict alterations in waking consciousness—including changes in mood, perception, experience of self and environment, and thought disorders—regardless of the inducing factor(s) (Dittrich 1996, 1998). Score-sums of the respective items make up the following five dimensions of the 5D-ASC: "oceanic boundlessness" (OB) measures derealization and depersonalization phenomena associated with positive emotional states ranging from heightened mood to euphoria. "Anxious ego dissolution" (AED) subsumes dysphoric mood states such as anxiety and fearful delusions, arising mainly from ego-disintegration and loss of self-control phenomena. The 5D-ASC main scale "visionary restructuralization" (VR) is constructed of items circumscribing

"elementary hallucinations," "synesthesia," "changed meaning of percept," "facilitated recollection," and "facilitated imagination." The "auditory alterations" (AA) scale summarizes acoustic phenomena empirically found during ASC, and the dimension "reduction of vigilance" (RV) depicts states of drowsiness and impairment of alertness and cognitive performance. The scale "global ASC score" (G-ASC) is constructed by addition of the scores from the OB, AED and VR subscales. Our subjects were asked to complete 5D-ASC rating scales 150 min and 300 min after drug administration and instructed to thereby rate their experience from the intervals 0–150 min and 150–300 min, respectively. To facilitate comparison of scales among each other, 5D-ASC data are presented as percentage values indicating percentage of maximum absolute scores.

Affective states

The adjective mood rating scale (AMRS) (Janke and Debus 1978) represents a multidimensional psychometric test developed for repeated measures of mood states. In practice, a list of 60 adjectives depicting mood states (e.g. "active," "lost in thought," "sociable") were presented to the subjects 10, 95 and 275 min and 24 h after drug intake. The volunteers were instructed to choose from four possible answers ("not at all," "somewhat," "quite," or "strongly" appropriate) to rate gradually to what extent each adjective characterizes their actual mood state. The AMRS consists of 15 subscales that can be subsumed interpretatively to seven domains of affective states: performance-related activity (efficiency-activation and concentration), general inactivation (inactivation, tiredness and drowsiness), extroversion-introversion (extroversion plus inverted scores from the introversion scale), general well being (self-confidence and heightened mood), emotional excitability (excitability, sensitivity and aggressiveness), anxiety-depressiveness (anxiety and depressed mood), and dreaminess.

Frankfurt attention inventory

Dose-dependent effects of PY on sustained attention were assessed 140 min after drug administration using the Frankfurt Attention Inventory (FAIR; Moosbrugger and Oehlschlägel 1996). This paper and pencil test measuring concentration behavior consists of 640 stimuli with high similarity that have to be discriminated against each other within 6 min. The FAIR test quantifies aspects of concentration behavior displayed in four test scores: "marker value" (MV) expresses comprehension of test instructions, "performance value" (PV) informs on the amount of attentively processed test items during a defined test period, "quality value" (QV) depicts the amount of attentively made decisions respective to the total amount of decisions, and the "continuity value" (CV) reflects the extent of continuously upheld concentration over the entire test duration. The FAIR task provides good test–retest reliability expressed as a Crohnbachs alpha between 0.85 and 0.91.

Physiological measures

Electrocardiogram

Electrocardiograms (EKG) were continuously registered for 24 h by use of a portable two-channel Holter recorder, model 90205, supplied by Spacelabs, Burdick. EKG monitoring was started 1 h before drug application, and the subjects were instructed to stop the recorder and remove the electrodes the following day. Signal quality was monitored with a Cardysuny 501X multichannel electrocardiograph (Fukuda ME, Kogyo, Japan), and data analysis was performed using a medical computer Model 90104A from Spacelabs, Burdick. The following EKG standard parameters were examined: mean, minimum and maximum heart rates (min^{-1}), number of supraventricular and ventricular extrasystoles (n), maximum S-T elevation (mm and °), maximum S-T depression (mm and °), and number of pauses (asystoles; n).

Blood pressure and body temperature

Blood pressure was measured using a Riva-Rocci sphygmanometer (Erka, Switzerland) 30 min before drug intake and at 5, 30, 60, 90, 120, 165 and 210 min. The axillary body temperature was recorded at the same time points using a Terumo digital clinical thermometer C2O2.

Blood pressure data expressed as mean arterial pressure (MAP) values were calculated as follows: MAP (mm Hg) = diastolic blood pressure + 1/3 (systolic blood pressure − diastolic blood pressure). Maximum rise of MAP above PL (PL values averaged from 0–210 min post-drug administration) is indicated as Δ MAX MAP.

Blood sampling, blood chemistry, and analysis of hormones

Blood samples for quantification of hormones and clinical-chemical parameters were drawn from an indwelling intravenous catheter into vacutainer tubes 20 min before drug administration and at 105 min and 300 min. Plasma was separated by centrifugation (15 min at 3000 rpm) immediately after sampling and stored at −27°C until analysis. The following blood parameters were later determined at the Institute of Clinical Chemistry of the University Hospital of Zürich: sodium (Na^+), potassium (K^+), chloride (Cl^-), urea (UR), creatinine (CR), lactate dehydrogenase (LDH), gamma glutamyltransferase (GGT), alkaline phosphatase (AP), aspartate aminotransferase (ASAT), alanine aminotransferase (ALAT), thyroid-stimulating hormone (TSH), prolactin (PRL), cortisol (CORT), and adrenocorticotropic hormone (ACTH). Besides sampling into EDTA-containing vacutainer tubes, blood samples for quantification of ACTH were additionally stabilized by adding 2000 KIU of aprotinin (Trasylol). Analytical methods used for quantification of clinical-chemical parameters and accuracies for the respective assays were as follows: Kinetic Jaffé-reaction (CR; accuracy 1.7% CV) (Bonini et al. 1992), enzyme-kinetic assays (LDH; CV 2.9%) (Knedel et al. 1986), GGT (CV 0.4%) (Bonini et al. 1992), ASAT (CV 3.1%) (Bonini et al. 1992), ALAT (CV 2.4%) (Bonini et al. 1992), and AP (CV 2.5%) (Knedel et al. 1986), ion-selective potentiometric assays (Na^+; CV 0.5%), K^+ (CV 1.0%) and Cl^- (CV 0.8%) (Bonini et al. 1992), electro-chemiluminescence technology (TSH; CV 3.9%) and CORT (CV 2.8%), chemiluminescence immunometric methods (ACTH; CV 8.8%) and PRL (CV 9.6%) (Robinson and Nelson 1983), and urease-GLDH assay (UR; CV 2.6%) (Bonini et al. 1992). Additional standard hematology analysis, including automated complete blood counts, was performed prior to the first and at the end of the last experimental day.

Statistical analysis

All statistical calculations were performed using the STATISTICA for windows software, version 6.0. According to the within-subject design of the study, every subject served as her/his own control in order to minimize effects of intraindividual variation in physiological and psychological test scores. Univariate two-way ANOVAs with treatment (PL and four doses of PY) and observation time as repeated measures were used to reveal differences between PL and drug conditions for all parameters. When significant main effects or interactions were detected with the ANOVA procedure, post-hoc pair-wise comparisons were performed using the Tukey HSD tests. Significance levels of main effects are cited in the text. Probability values of $P<0.05$ were considered statistically significant.

Trapezoid calculation of AUC values ("Area under the data–time curve") for analysis of blood pressure and body temperature data was performed in Microsoft Excel 2000, using the equation

$$\mathrm{AUC}_{(0-t)} = \sum_{i=0}^{n-1} \frac{t_{i+1} - t_i}{2} \left(MAP_i + MAP_{i+1}\right).$$

Results

Acute psychological effects of psilocybin

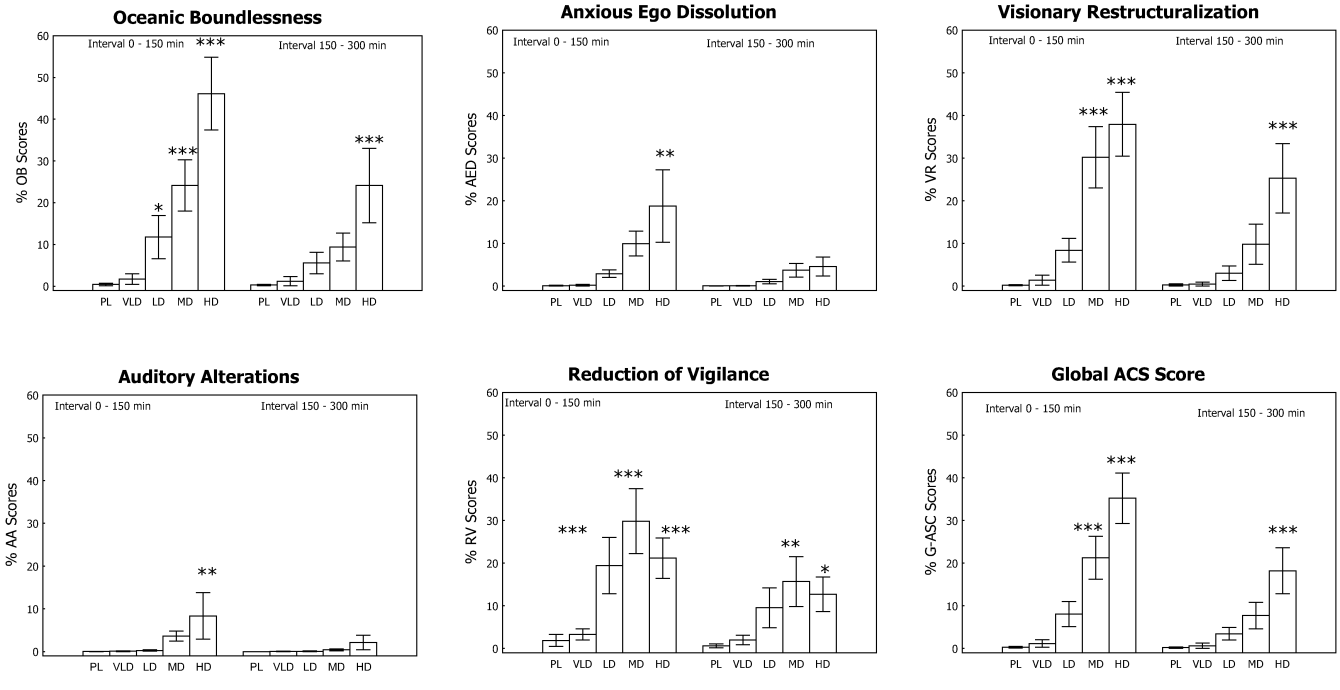
First subjective changes were perceived by the volunteers usually 20–40 min following administration of PY. Peak effects were reported after 60–90 min, lasting for another 60–120 min. PY effects then gradually subsided and were completely worn off at the 6-h point. Already, the threshold dose of 45 µg/kg PY (VLD) was rated clearly psychoactive by most of our volunteers. Slight drowsiness and increased sensitivity and intensification of pre-existing mood states were most prominent effects at this dosage level. LD, MD and HD PY (115, 215 and 315 µg/kg) dose dependently induced changes in mood states, sensory perception (including colorful visual illusions, complex scenic hallucinations and synesthesias), as well as alterations in perception of time, space, and self. Typically, the experiences after MD and HD PY were rated positive, with retrospective statements ranging from "pleasurable" to "ineffably beautiful." "Magic" or "phantasmagoric" were terms often used to circumscribe a PY experience. However, one volunteer (male, 23 years) reacted with pronounced anxiety to HD PY. He reported a fearful experience marked by depressed mood and fear of losing control. Without pharmacological intervention, his anxiety during the plateau phase of PY action gradually subsided and the dysphoric reaction was completely resolved six hours post-drug ingestion.

Dimensions of ASC

Figure 1 shows detailed psychometric data from the 5D-ASC rating scale regarding four doses of PY compared with PL condition. As assessed by both rating intervals (0–150 min and 150–300 min after drug administration), PY dose dependently increased scores of all 5D-ASC scales [main effect of drug: OB ($F_{4,28}$=8.58, P<0.001), VR ($F_{4,28}$=7.26, P<0.001), AA ($F_{4,28}$=2.72, P<0.05), RV ($F_{4,28}$=3.07, P<0.05), G-ASC ($F_{4,28}$=8.85, P<0.001)], whereas for the dimension "anxious ego dissolution" a significance level of P<0.05 was just missed [AED ($F_{4,28}$=2.39, P<0.07)]. When calculated with mean scores from our eight subjects, least-squares linear regressions show excellent linearity between PY dose and scores of the three core 5D-ASC dimensions (OB, AED, VR) as well as the Global ASC score G-ABZ. Correlation coefficients (r) of the linear regression models of the examined rating interval 0–150 min were 0.98 for OB (P<0.003), 0.97 for AED (P<0.005), 0.98 for VR (P<0.004), and 0.99 for G-ABZ (P<0.002), respectively.

Affective states

Table 1 summarizes time- and dose-dependent effects of PY on affective states, as assessed with the AMRS. A three-way ANOVA revealed significant AMRS scale × treatment × time interaction ($F_{72,504}$=1.68, P<0.001). Subsequent post-hoc analysis showed significant increas-



*p<.05, **p<.01, ***p<.001 compared to placebo condition (Tukey HSD post hoc test).

Fig. 1 Subjective effects of psilocybin. Percentage scores from the altered states of consciousness rating scale 5D-ASC (mean±SEM, n=8). Scores indicate percentage of theoretical scale maxima

Table 1 Subjective effects of psilocybin. Dose-dependent scores in the seven domains of affective states from the adjective mood rating scale (AMRS) (mean±SEM, *n*=8)

	Placebo	Psilocybin VLD (45 μg/kg)	Psilocybin LD (115 μg/kg)	Psilocybin MD (215 μg/kg)	Psilocybin HD (315 μg/kg)
Rating 1 (baseline)					
Performance-related activity	19.1±1.4	19.3±1.0	18.9±1.7	17.4±0.7	16.6±1.4
General inactivation	16.5±1.6	15.0±2.2	16.3±2.3	13.9±1.0	17.6±2.6
Extroversion-introversion	4.4±1.1	4.6±0.9	5.1±1.1	3.5±0.6	3.0±0.9
General well being	20.0±1.7	20.3±1.2	22.6±1.4	19.5±1.9	18.6±2.2
Emotional excitability	15.4±0.7	15.3±0.7	15.6±1.1	16.5±1.0	16.7±1.7
Anxiety-depressiveness	8.3±0.2	9.0±0.8	8.0±0.0	9.0±0.6	9.9±1.1
Dreaminess	6.3±0.8	6.4±0.7	5.9±0.6	6.0±0.5	5.9±0.7
Rating 2 ($t_{0+95\ min}$)					
Performance-related activity	17.8±1.2	16.4±0.9	15.1±1.4	14.9±1.2	14.9±1.7
General inactivation	14.6±1.8	18.0±2.5	21.0±2.2	23.5±1.9***	24.9±2.0***
Extroversion-introversion	5.3±0.7	2.8±1.4	1.9±1.2	0.3±1.7**	−1.9±1.4***
General well being	18.6±1.9	20.4±1.5	20.9±1.8	22.4±2.0	22.0±2.5
Emotional excitability	14.9±1.3	15.0±0.9	15.0±0.9	17.8±1.7	20.6±2.2***
Anxiety-depressiveness	9.0±0.7	8.6±0.5	8.7±0.4	8.9±0.4	11.6±2.6
Dreaminess	6.4±0.7	7.3±0.9	7.6±0.7	11.6±1.0***	10.6±0.8***
Rating 3 ($t_{0+275\ min}$)					
Performance-related activity	18.3±1.3	17.8±1.2	16.3±1.0	16.6±0.8	16.0±0.9
General inactivation	13.6±0.7	16.0±2.1	17.0±1.5	17.0±1.7	21.6±2.3**
Extroversion-introversion	4.8±1.0	4.6±0.9	2.7±1.1	2.0±1.4	1.6±1.6
General well being	19.6±1.9	20.1±1.5	21.1±1.6	21.1±1.3	22.6±1.3
Emotional excitability	14.6±0.9	14.9±1.6	15.1±1.1	15.5±1.2	15.7±1.2
Anxiety-depressiveness	8.3±0.3	8.5±0.5	8.6±0.4	8.4±0.4	8.7±0.5
Dreaminess	6.0±0.7	6.4±0.9	6.7±0.8	7.3±0.9	10.6±0.5***
Rating 4 ($t_{0+24\ h}$)					
Performance-related activity	19.7±1.1	20.0±1.3	20.6±1.2	18.7±1.1	16.3±1.3
General inactivation	14.0±0.7	14.3±0.9	14.7±0.9	18.4±2.0	18.7±1.4
Extroversion-introversion	5.4±1.0	5.3±0.6	5.3±0.3	3.0±1.1	1.4±1.8
General well being	19.7±1.7	19.8±1.3	21.0±0.9	18.7±1.0	17.9±1.3
Emotional excitability	15.9±1.1	14.8±1.3	15.4±0.9	15.3±1.5	16.4±0.9
Anxiety-depressiveness	9.4±0.7	8.4±0.4	8.9±0.5	9.3±0.7	10.6±1.1
Dreaminess	5.1±0.5	5.1±0.5	5.6±0.7	7.3±1.0	8.4±0.8**

* $P<0.05$
** $P<0.01$
*** $P<0.001$ compared with placebo condition (Tukey HSD post-hoc test)

es in the AMRS dimensions "general inactivation" (PY 215 μg/kg, t_0+95 min: $P<0.001$; PY 315 μg/kg, t_0+95 min: $P<0.001$ and PY 315 μg/kg, t_0+275 min: $P<0.01$), "emotional excitability" (PY 315 μg/kg, t_0+95 min: $P<0.001$) and "dreaminess" (PY 215 μg/kg, t_0+95 min: $P<0.001$; PY 315 μg/kg, t_0+95 min: $P<0.001$; PY 315 μg/kg, t_0+275 min: $P<0.001$ and PY 315 μg/kg, t_0+24 h: $P<0.01$), relative to PL. Increased introversion at the peak of the drug effect (t_0+95 min) is reflected by significantly decreased scores on the AMRS scale "extroversion-introversion" (PY 215 μg/kg: $P<0.01$ and PY 315 μg/kg: $P<0.001$).

Frankfurt attention inventory

PY exerted no significant influence on the FAIR scores MV ($F_{4,28}$=0.58, P=0.687) and QV ($F_{4,28}$=1.39, P=0.261). In contrast, administration of PY led to a significant decrease in the FAIR scores PV ($F_{4,28}$=12.28, $P<0.00001$) and CV ($F_{4,28}$=11.23, $P<0.00001$) as shown in Table 2. Thereby PV and CV were not significantly influenced by VLD and LD PY, whereas MD and HD PY decreased the respective scores to approximately 50% of values obtained under PL condition.

Acute physiological effects of psilocybin

Electrocardiogram

ANOVA calculations revealed no differences in any of the examined parameters of the Holter-24 h EKG. No evidence for a PY-induced change of cardiac electrophysiology was found. In Table 3, all EKG results and F and P values from the respective statistical calculations are resumed. In order to compactly display the EKG results, all data were classed in three intervals: the baseline interval ("interval 1"; $t_{0-1\ h}$–t_0), the interval of acute effects of PY ("interval 2"; t_0–$t_{0+6\ h}$), and the interval covering the time from the end of subjective drug action up to 24 h ("interval 3"; $t_{0+6\ h}$–$t_{0+24\ h}$).

Table 2 Effects of psilocybin on sustained attention. Scores from the Frankfurt attention inventory (FAIR; mean±SEM, *n*=8)

	Placebo	Psilocybin VLD (45 μg/kg)	Psilocybin LD (115 μg/kg)	Psilocybin MD (215 μg/kg)	Psilocybin HD (315 μg/kg)
Rating at 140 min post-drug ingestion					
Marker value (MV)	0.991±0.003	0.991±0.003	0.993±0.003	0.984±0.009	0.987±0.002
Performance value (PV)	480.6±33.4	456.5±25.8	455.8±31.9	260.7±25.0 ***	258.0±42.0 ***
Quality value (QV)	0.943±0.014	0.959±0.014	0.961±0.004	0.927±0.029	0.910±0.025
Continuity value (CV)	455.9±34.4	438.9±28.0	439.4±32.3	242.6±27.0 ***	243.6±43.3 ***

*P<0.05
**P<0.01
***P<0.001 compared with placebo condition (Tukey HSD post-hoc test)

Table 3 Electrocardiographic data following placebo and four doses of psilocybin (mean±SEM, *n*=8)

	Placebo	Psilocybin VLD (45 μg/kg)	Psilocybin LD (115 μg/kg)	Psilocybin MD (215 μg/kg)	Psilocybin HD (315 μg/kg)	Main effect of drug F (4, 28) values	Main effect of drug P values
Interval 1 (baseline; $t_{0-1\ h}$–t_0)							
Mean heart rate (min^{-1})	78±5	79±5	75±3	85±6	82±6	0.601	0.665
Minimum heart rate (min^{-1})	57±4	62±3	58±3	60±4	65±4	0.589	0.673
Maximum heart rate (min^{-1})	126±6	120±6	130±5	130±7	112±7	2.280	0.086
Supraventricular extrasystoles (n)	1±1	1±1	1±1	1±1	1±1	2.058	0.114
Ventricular extrasystoles (n)	2±1	1±1	2±2	1±1	1±1	2.492	0.067
Maximum S-T elevation (mm)	1.3±0.4	2.0±0.4	2.5±0.5	1.6±0.3	1.6±0.2	1.570	0.210
Maximum S-T elevation (slope, °)	27±7	45±8	46±5	46±4	37±6	1.230	0.321
Maximum S-T depression (mm)	0.3±0.2	−0.1±0.2	−0.3±0.3	−0.2±0.5	0.0±0.2	0.918	0.467
Maximum S-T depression (slope, °)	10±4	17±6	18±6	18±5	14±4	1.178	0.341
Pauses (n)	0±0	0±0	0±0	0±0	0±0	0.148	0.963
Interval 2 (t_0 –$t_{0+6\ h}$)							
Mean heart rate (min^{-1})	85±5	82±5	82±5	87±6	84±4		
Minimum heart rate (min^{-1})	60±4	62±4	61±2	60±3	63±2		
Maximum heart rate (min^{-1})	141±5	128±6	137±8	140±8	131±6		
Supraventricular extrasystoles (n)	21±6	7±3	19±9	5±2	4±3		
Ventricular extrasystoles (n)	16±7	2±2	5±4	5±3	3±2		
Maximum S-T elevation (mm)	1.5±0.4	2.2±0.6	2.6±0.5	1.9±0.3	1.6±0.3		
Maximum S-T elevation (slope, °)	35±8	46±8	49±5	50±4	43±7		
Maximum S-T depression (mm)	0.0±0.2	−0.4±0.3	−0.4±0.3	−0.4±0.3	−0.2±0.1		
Maximum S-T depression (slope, °)	8±4	16±6	14±8	20±6	13±4		
Pauses (n)	0±0	0±0	0±0	0±0	0±0		
Interval 3 ($t_{0+6\ h}$ –$t_{0+24\ h}$)							
Mean heart rate (min^{-1})	73±3	74±5	70±4	77±5	72±2		
Minimum heart rate (min^{-1})	55±3	60±4	53±3	55±2	55±1		
Maximum heart rate (min^{-1})	121±2	115±6	118±2	116±6	111±2		
Supraventricular extrasystoles (n)	9±3	11±5	10±3	4±1	8±4		
Ventricular extrasystoles (n)	8±3	6±3	6±2	4±2	7±3		
Maximum S-T elevation (mm)	1.1±0.3	2.1±0.6	2.0±0.4	1.8±0.3	1.6±0.3		
Maximum S-T elevation (slope, °)	25±6	38±7	40±5	40±4	34±5		
Maximum S-T depression (mm)	0.2±0.2	0.0±0.2	-0.5±0.5	-0.3±0.5	0.3±0.2		
Maximum S-T depression (slope, °)	10±4	16±6	14±6	18±5	14±4		
Pauses (n)	1±1	1±1	1±1	1±1	1±1		

Blood pressure and body temperature

No statistically significant main effect of PY on MAP ($F_{4,28}$=1.81, P=0.155), maximum rise of MAP above averaged PL values (Δ MAX MAP; $F_{3,21}$=1.04, P=0.396), and area under the MAP–time curve ($AUC_{(0-t)}$ MAP; $F_{4,28}$=2.43, P=0.071) was found. ANOVA analysis, however, detected a significant dose × time interaction ($F_{28,196}$=2.34, P=0.0004). As depicted in Fig. 2a, b, a trend of PY to increase blood pressure is apparent. Subsequent post-hoc tests revealed that blood pressure (systolic blood pressure and MAP) was significantly increased only 60 min following administration of HD PY, relative to PL (P<0.001). Diastolic blood pressure was significantly elevated (P<0.05) only 90 min following intake of HD PY. Time courses of averaged MAP values following four doses of PY and PL are shown in

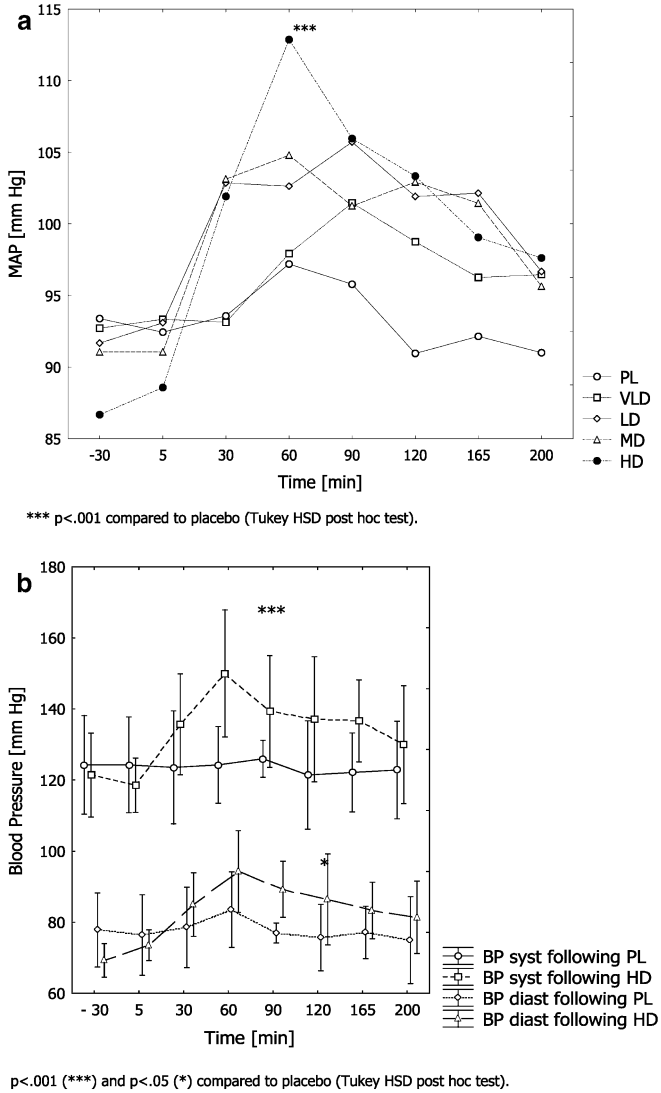


Fig. 2 **a** Average mean arterial blood pressure (*MAP*) following four doses of psilocybin and placebo, respectively (n=8). **b** Systolic and diastolic blood pressures following administration of placebo and HD psilocybin (mean±SEM, n=8)

Fig. 2a, and systolic and diastolic blood pressure following HD PY and PL are depicted in Fig. 2b.

Axillary body temperature was not significantly influenced by any of the applied doses of PY ($F_{4,28}$=0.94, P=0.452). ANOVA of the corresponding area under the data–time curves also did not reveal statistical differences between the groups. Effects of PY on blood pressure and body temperature are summarized in Table 4.

Neuroendocrine data

ANOVA of the hormone plasma concentrations revealed a statistically significant main effect of drug only for PRL ($F_{4,28}$=6.41, P=0.0009), whereas significant dose × time interactions were found for all monitored hormones (TSH: $F_{8,56}$=3.95, P=0.0009; PRL: $F_{8,56}$=4.68, P=0.0002; ACTH: $F_{8,56}$=4.23, P=0.0005; and CORT: $F_{8,56}$=2.43, P=0.025). Tukey HSD post-hoc pairwise comparison with corresponding values after PL treatment revealed significantly elevated plasma levels for all measured parameters in blood samples collected 105 min following HD PY (TSH following PY 315 µg/kg, P<0.01; PRL following PY 315 µg/kg, P<0.001; ACTH following PY 315 µg/kg, P<0.01; and CORT following PY 315 µg/kg, P<0.05). PRL plasma concentrations were already increased following MD PY (PRL following PY 215 µg/kg, P<0.01). In the plasma samples collected 300 min post-drug administration, all hormone concentrations were back to pre-dose levels. Detailed data for time- and dose-dependent effects of PY on plasma levels of hormones are given in Table 5.

Blood chemistry and hemogram

With the exception of two liver enzymes determined in plasma samples taken 105 min following administration of HD PY (ASAT and GGT; see beneath), PY did not elicit statistically significant responses from any of the analyzed clinical-chemical blood parameters. Mean plasma concentrations of all monitored compounds as well as F and P values deriving from ANOVA calculations of main effects of drug are summarized in Table 6. Statistically significant drug × time interactions were found

Table 4 Effects of psilocybin on blood pressure and body temperature (mean±SEM, n=8)

	Placebo	Psilocybin VLD (45 µg/kg)	Psilocybin LD (115 µg/kg)	Psilocybin MD (215 µg/kg)	Psilocybin HD (315 µg/kg)
MAP[1]	93±3.9	97±3.9	101±3.6	100±4.2	101±3.9
Δ MAX MAP[2]	–	14±4.4	16±4.7	15±3.9	21±5.3
AUC $_{(0-t)}$ MAP[3]	21447±883	22199±853	23069±926	22935±983	23158±981
Body temp (°C)	36.5±0.1	36.6±0.1	36.4±0.2	36.5±0.1	36.6±0.1
AUC $_{(0-t)}$ temp[4]	8394±31	8428±16	8370±36	8408±21	8418±28

[1] Averaged mean arterial pressure (mmHg; 5–210 min post-drug administration)
[2] Maximum rise of MAP above averaged placebo values (mmHg)
[3] Area under the MAP–time curve (mmHg × min)
[4] Area under the body temperature–time curve (°C × min)

Table 5 Neuroendocrine effects of psilocybin. Dose-dependent plasma concentrations of hormones (mean±SEM, *n*=8)

	Placebo	Psilocybin VLD (45 µg/kg)	Psilocybin LD (115 µg/kg)	Psilocybin MD (215 µg/kg)	Psilocybin HD (315 µg/kg)
Sampling 1 (baseline, $t_{0-20\ min}$)					
Thyroid-stimulating hormone (TSH [mU/l])	1.30±0.15	1.62±0.13	1.54±0.13	1.40±0.16	1.27±0.14
Prolactin (PRL [µg/l])	16.7±5.5	16.0±5.4	14.6±4.3	15.5±5.7	14.8±2.8
Adrenocorticotropic hormone (ACTH [ng/l])	21±6	17±5	17±4	18±6	12±2
Cortisol (CORT [nmol/l])	432±59	336±54	378±77	382±50	385±71
Sampling 2 ($t_{0+105\ min}$)					
Thyroid-stimulating hormone (TSH [mU/l])	1.24±0.16	1.41±0.09	1.50±0.13	1.54±0.16	1.66±0.22**
Prolactin (PRL [µg/l])	9.5±2.0	12.8±4.6	14.5±5.3	22.4±7.7**	28.0±7.5***
Adrenocorticotropic hormone (ACTH [ng/l])	20±5	19±4	25±5	42±14	50±12**
Cortisol (CORT [nmol/l])	348±50	353±85	443±47	522±82	567±74*
Sampling 3 ($t_{0+300\ min}$)					
Thyroid-stimulating hormone (TSH [mU/l])	1.16±0.15	1.38±0.19	1.15±0.09	1.20±0.13	1.18±0.18
Prolactin (PRL [µg/l])	12.4±2.7	9.0±1.6	9.1±1.7	9.7±2.0	12.9±2.9
Adrenocorticotropic hormone (ACTH [ng/l])	18±4	15±3	15±2	14±2	15±2
Cortisol (CORT [nmol/l])	353±54	306±64	289±60	294±57	344±61

* $P<0.05$
** $P<0.01$
*** $P<0.001$ compared with placebo condition (Tukey HSD post-hoc test)

only for the liver enzymes ASAT ($F_{8,56}$=2.26, P=0.036) and GGT ($F_{8,56}$=2.15, P=0.046). Consecutive post-hoc pairwise comparison revealed significantly elevated concentrations of these two parameters in the plasma samples collected 105 min following administration of HD PY (ASAT $P<0.001$; GGT $P<0.002$), relative to PL.

Comparison of hemograms from blood samples preceding the first and following the last experimental day revealed no differences whatsoever in any parameter. None of the hematological parameters of any subject was out of normal range.

Discussion

Acute psychological effects of psilocybin

Psilocybin (PY) dose dependently induced important alterations of perception, affect, ego-functions, and attention in all subjects. The phenomenological concept of ego-functions (e.g., ego-identity, ego-vitality, ego-demarcation, etc.) and their perturbations in the course of ASC or psychopathology is explained by Scharfetter (1981). Analysis of the 5D-ASC scores revealed that only MD and HD PY led to a relevant loosening of ego-boundaries (OB/AED) and to pronounced changes of perception (VR). The loosening of the demarcation between self and environment was generally accompanied by insight and experienced as "touching" or "unifying with a higher reality" (OB). In one subject, however, HD PY transiently led to a disturbance of ego functions that was experienced with pronounced anxiety (AED). Also, only MD and HD PY induced intermittent geometric and complex visual hallucinations, whereas VLD and LD PY led to illusions in terms of intensification or distortion of visual perception (VR). PY also amplified or altered acoustic perception (AA), but no auditory hallucinations occurred during any of the experiments. All PY-induced symptoms were worn off completely 6–8 h after drug administration.

As expressed in scores from the AMRS mood rating scale, increased general inactivation, introversion, and dreaminess were seen robustly in all subjects. A statistically significant increase in the AMRS subscale "dreaminess" was still present in the rating 24 h following administration of HD PY, presumably representing the need to reflect and integrate the content of a profound hallucinogen experience well into the next day. Administration of both VLD and LD PY induced a mental condition described by one volunteer as "switching between the worlds". In this state, normal waking consciousness is intermittently pervaded with transient and unstable drug states in a wavelike pattern, but the "insightfulness" typically experienced after higher doses of PY is absent. When distinct hallucinogenic effects were perceived following the two lower doses, they were short lasting and only present for about 1–2 h. The effect–time course following VLD PY supports our previous findings (Hasler 1997; Hasler et al. 1997), that PY effects arise and wear off with a certain blood level of PI (approximately 4–6 ng PI/ ml plasma). This opposes the alternative hypothesis that PY might initiate secondary downstream brain mechanisms whose subjective effects could well outlast the presence of pharmacologically relevant amounts of the active compound in the bloodstream. We abstained from monitoring plasma concentration–time profiles of PI, since reliable determination of this highly unstable phenolic compound requires a sophisticated and costly analysis technique (Hasler et al. 1997; Lindenblatt et al. 1998).

Interestingly, several subjects could not clearly state in retrospect on which experimental day they had received

Table 6 Plasma concentrations of clinical chemical parameters following administration of four doses of psilocybin (mean±SEM, *n*=8)

	Placebo	Psilocybin VLD (45 µg/kg)	Psilocybin LD (115 µg/kg)	Psilocybin MD (215 µg/kg)	Psilocybin HD (315 µg/kg)	Main effect of drug *F* (4, 28) values	Main effect of drug *P* values
Sampling 1 (baseline, $t_{0-20\ min}$)							
Natrium (Na^+ [mmol/l])	139±2	140±1	141±1	139±2	140±1	0.764	0.558
Potassium (K^+ [mmol/l])	4.0±0.1	3.9±0.1	4.0±0.1	4.0±0.1	4.0±0.1	0.891	0.482
Chloride (Cl^- [mmol/l])	109±3	104±3	100±3	102±5	108±3	2.053	0.114
Urea (UR [mmol/l])	4.2±0.4	5.1±0.6	4.6±0.4	4.6±0.6	4.3±0.3	2.220	0.093
Creatinine (CR [µmol/l])	83±6	87±6	82±4	82±4	83±4	0.732	0.578
Lactate dehydrogenase (LDH [U/l])	272±13	308±18	295±20	295±21	285±13	2.028	0.118
γ-Glutamyltransferase (GGT [U/l])	13±1	13±1	13±1	13±1	13±2	1.380	0.266
Aspartate aminotransferase (ASAT [U/l])	16±2	18±1	17±2	18±2	16±1	1.548	0.206
Alanine aminotransferase (ALAT [U/l])	13±1	14±2	15±2	16±3	13±1	1.490	0.232
Alkaline phosphatase (AP [U/l])	74±9	75±11	78±11	76±11	71±10	0.347	0.844
Sampling 2 ($t_{0+105\ min}$)							
Natrium (Na^+ [mmol/l])	138±3	139±1	140±1	138±3	140±1		
Potassium (K^+ [mmol/l])	3.8±0.1	3.8±0.1	4.0±0.1	4.0±0.1	4.0±0.1		
Chloride (Cl^- [mmol/l])	108±2	103±2	100±1	104±3	107±2		
Urea (UR [mmol/l])	4.0±0.4	4.9±0.6	4.4±0.3	4.2±0.5	4.0±0.3		
Creatinine (CR [µmol/l])	79±6	82±4	84±5	78±5	72±3		
Lactate dehydrogenase (LDH [U/l])	265±18	306±17	318±29	329±30	331±20		
γ-Glutamyltransferase (GGT [U/l])	13±2	13±1	13±2	14±1	16±3**		
Aspartate aminotransferase (ASAT [U/l])	16±2	18±2	19±2	19±2	24±3***		
Alanine aminotransferase (ALAT [U/l])	13±2	15±1	16±2	16±2	18±3		
Alkaline phosphatase (AP [U/l])	74±9	76±10	78±11	83±12	80±12		
Sampling 3 ($t_{0+300\ min}$)							
Natrium (Na^+ [mmol/l])	137±3	140±1	140±1	138±3	141±1		
Potassium (K^+ [mmol/l])	3.8±0.1	3.8±0.1	3.9±0.1	3.9±0.1	3.8±0.1		
Chloride (Cl^- [mmol/l])	104±3	104±2	101±2	103±3	109±2		
Urea (UR [mmol/l])	3.7±0.3	4.6±0.6	4.0±0.3	3.9±0.4	3.7±0.3		
Creatinine (CR [µmol/l])	76±6	80±4	82±4	78±4	78±3		
Lactate dehydrogenase (LDH [U/l])	271±13	315±11	309±16	317±21	302±13		
γ-Glutamyltransferase (GGT [U/l])	12±1	13±1	13±1	14±1	15±2		
Aspartate aminotransferase (ASAT [U/l])	16±2	19±3	19±3	18±2	20±2		
Alanine aminotransferase (ALAT [U/l])	13±2	15±2	16±2	14±2	17±2		
Alkaline phosphatase (AP [U/l])	76±10	79±10	81±12	78±11	77±10		

* $P<0.05$
** $P<0.01$
*** $P<0.001$ compared with placebo condition (Tukey HSD post-hoc test)

VLD and LD PY, or MD and HD PY, respectively. The fact that VLD and LD PY as well as MD and HD PY have common "qualities" in respect of subjective effects is also mirrored in the results from the FAIR attention test. Individual scores for the "performance value" and "continuity value" were almost identical following VLD and LD PY, and MD and HD PY, respectively. Following MD and HD PY, both FAIR scores were reduced to roughly 50% of the scores reached after PL, VLD, or LD PY. The strongly impaired performance in the FAIR test under MD and HD PY is difficult to appraise, since the obvious reduction of attentional abilities due to $5\text{-}HT_{2A}$ receptor overstimulation may well be confounded by the (also drug-induced) lack of motivation to perform well in this task, as stated by several subjects.

Scores from the 5D-ASC dimension RV indicate that vigilance is reduced less following HD PY than after MD PY. We propose that following PY in a dosage of 315 µg/kg body weight, noradrenergic neurotransmission is significantly stimulated as well, leading to an overcompensation of the more inactivating effects of predominantly 5-HT stimulation induced by lower PY doses. This reasoning is in line with the hypothesis that hallucinogen-induced inhibition of Raphe neurons leads to an increased activity of adjacent noradrenergic neurons of the locus coeruleus (Marek and Aghajanian 1998; Aghajanian and Marek 1999).

Acute physiological effects of psilocybin

Due to its general use for clinical purposes, effects of PY on blood pressure are mainly presented as MAP values (Table 4), representing the average blood pressure during a cardiac cycle. Maximum rises of MAP above averaged PL MAP values within 210 min following drug administration were calculated for every dosage level of PY and labeled Δ MAX MAP. Corresponding absolute peak MAP values for every PY dosage level can be calculated by simple addition of the averaged MAP value following PL (93 mmHg; Table 4) and the Δ MAX MAP value of the respective PY dose. For example, the averaged absolute peak MAP value after administration of HD PY was 114 mmHg (93 mm MAP for PL plus 21 mm Δ MAX MAP for HD). As shown in Fig. 2a, compared with PL, the MAP is significantly elevated only 60 min following ingestion of HD PY. Looking only at averaged values, the short-lasting elevation of blood pressure following HD PY is no cause for concern, but individual values can be considered critical. Maximum individual values for systolic and diastolic blood pressure registered 60 min following application of HD PY were 180/110 mmHg (female, 29 years) and 170/120 mmHg (male, 24 years), respectively. Detailed inspection of the psychometric scales 5D-ASC and AMRS as well as personal reports gave no evidence for excessive stress or anxiety at this time point. By contrast, subject 4 (male, 23 years), who reported great anxiety, did not have significantly elevated blood pressure. The increase of MAP during peak effects of HD PY is not surprising because cardiovascular regulation is partially mediated by central 5-HT_2 and 5-HT_{1A} receptor activation (Ramage 2001). As a completion to the "Δ MAX MAP" parameter describing momentary and short-lasting blood pressure peaks, comparison of "Areas under the MAP–time curve" ($AUC_{(0–t)}$ MAP) allows a quantitative assessment of changes in blood pressure over the entire duration of PY action. None of the applied doses of PY led to $AUC_{(0–t)}$ MAP values different from the $AUC_{(0–t)}$ MAP value calculated from PL data. Despite the possibility of a short-lasting moderate elevation of blood pressure, in healthy humans without pre-existing medical conditions, no cardiovascular complications must be expected from administration of PY.

As shown in Table 5, administration of PY led to an increase of plasma concentrations of all analyzed hormones (TSH, PRL, ACTH, and CORT) in samples collected 105 min following drug administration, i.e., during peak effects of PY. PY-induced changes in plasma levels of TSH, PRL, ACTH and CORT have not been previously reported. By the 300-min point, all endocrine parameters were back to baseline values. Due to a pronounced variability in plasma levels, statistically significant differences in plasma concentrations relative to the PL condition were reached for all hormones only following HD PY, and for PRL also following MD PY. It is noteworthy that only PRL levels in plasma samples taken 105 min post-HD PY (28.0±7.5) were out of the normal physiological range (3.4–24.1 μg/l). Taking into account that CORT plasma levels follow a circadian rhythm, it is difficult to distinguish between drug effect and physiological daily fluctuations. The effect of circadian endocrine fluctuation was controlled to some degree by starting the experiments at the same time each day. It is unlikely that increased ACTH and CORT plasma concentrations following HD PY are an expression of stress, because no correlation between CORT levels and scores of the anxiety depicting 5D-ASC subscale AED (r=0.035) were found. An increase of ACTH and CORT plasma concentrations as a direct result of 5-HT_2 receptor stimulation is not surprising, because both animal and human studies suggest that pharmacological stimulation of 5-HT mechanisms activates the hypothalamo-pituitary-adrenal (HPA) axis, resulting in a release of ACTH and corticosteroids into the blood stream (Fuller 1981; Holmes et al. 1982; Van de Kar et al. 2001). Following 5-HT_2 receptor stimulation, hypothalamic neurosecretory transducer cells liberate corticotropin releasing hormone (CRH), leading to an increase of ACTH and CORT plasma concentrations. Our findings are in line with the results of a study by Gouzoulis-Mayfrank et al. (1999) comparing psychological and physiological effects of single moderate doses of D-amphetamine, 3,4-methylenedioxyethylamphetamine (MDE) and PY. In their investigation, administration of approximately 200 μg/kg PY also led to a statistically non-significant increase of CORT plasma concentrations. In contrast, their administration of MDE induced a robust increase of CORT plasma concentrations in all volunteers. These findings suggest that acute stimulation of 5-HT release (as it is caused by MDE), is more important for activation of the HPA-axis than direct agonistic action at the 5-HT_2 receptor.

PY-induced increase in 5-HT activity is also reflected by an elevation of PRL plasma levels following administration of MD and HD PY. This finding was not unexpected, because release of PRL from the anterior pituitary is controlled by inhibitory tuberoinfundibular dopaminergic neurons and by stimulatory 5-HT mechanisms (Prescott et al. 1984; Van de Kar et al. 1985). That is, dorsal raphe nucleus 5-HT neurons that project to the hypothalamus appear to be involved in the secretion of PRL (Meltzer and Nash 1988).

The finding of a moderate, but statistically significant increase of TSH plasma levels following administration of HD PY is difficult to interpret, because functional relationships between the hypothalamic-pituitary-thyroid (HPT) axis and 5-HT mechanisms are not well understood and still controversially discussed (Krulich 1982; Mannisto 1983; Duval et al. 1999). Some experimental findings from animal studies indicate that the central 5-HT system has an inhibitory influence on TSH secretion (Mitsuma and Nogimori 1983), whereas others propose the absence of a significant role for 5-HT in the physiological release of TSH (O'Malley et al. 1984). Yet other researchers suggest that 5-HT increases TSH release into the bloodstream, probably by increasing TRH

(thyroid-releasing hormone) production or by facilitating the pituitary TSH response to TRH (Silva and Nunes 1996). Our finding of elevated TSH blood levels following 5-HT_2 receptor challenge is consistent with the hypothesis of stimulation of the HPT axis by 5-HT mechanisms. Neuroendocrinological research studies using pre-treatment with selective 5-HT receptor agonists and antagonists might contribute to a better understanding of this issue.

Statistical analysis of plasma concentrations of a multitude of clinical chemical markers (Table 6) revealed that PY has an effect solely on two liver enzymes: ASAT and GGT. Thereby, only HD PY led to a statistically significant, although clinically irrelevant, short-term increase of these enzymes. It is noteworthy that also the transiently increased ASAT and GGT plasma concentrations were not out of normal physiological ranges [ASAT: 10–31 U/l (female) and 10–34 U/l (male); GGT: 7–32 U/l (female) and 11–50 U/l (male)]. In blood samples taken 300 min following HD PY, ASAT and GGT values were back to pre-dose levels and no longer significantly different from respective concentrations determined under the PL condition. We interpret the finding of a transient elevation of ASAT and GGT following HD PY as a sign of non-specific increase of liver enzyme activity as it is often seen in "liver sensitive" subjects following administration of a multitude of drugs (Fried 2000).

We see two methodological limitations for the present study. First, the moderate number of eight subjects may lead to some distortion of the results, whereby a putative bias is expected to be most pronounced for psychological variables. Parameters with small effect sizes are unlikely to reach the level of statistical significance and therefore minor effects, e.g., following lower doses of PY, could have been missed. Second, one might argue that the highest dose of PY (315 μg/kg) used in this study is not a "real" high dose, and some effects of PY would be clearly apparent only following higher doses of PY. To the best of our knowledge, no controlled clinical studies in humans have been conducted using higher doses of PY. For safety reasons, we decided to not use more PY because we were not willing to expose our subjects to a potentially more stressful drug effect at this early stage of investigations.

Conclusions

Our investigations provided no cause for concern that administration of PY to healthy subjects is hazardous with respect to somatic health. However, as our data revealed tendencies of PY to temporarily increase blood pressure, we advise subjects suffering from cardiovascular conditions, especially untreated hypertension, to abstain from using PY or PY-containing mushrooms. Furthermore, our results indicate that PY-induced ASC are generally well tolerated and integrated by healthy subjects. However, a controlled clinical setting is needful, since also mentally stable personalities may, following ingestion of higher doses of PY, transiently experience anxiety as a consequence of loosening of ego-boundaries.

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