HYPOTHESES

At the time when the present investigation was designed (end of 1996), virtually all data available on *ayahuasca* dealt only with its botany and chemistry. The only information on its effects in humans came from reports involving its self-administration by single subjects and no data were available regarding its acute administration to healthy humans in controlled studies. The following hypotheses were postulated:

1. The administration of *ayahuasca* to healthy humans would elicit dose-dependent subjective effects characteristic of psychedelics.

2. The access of *ayahuasca* alkaloids to the CNS would be measurable by means of quantitative pharmaco-electroencephalography (q-EEG).

3. Discrete brain regions would be identified by means of Low Resolution Electromagnetic Tomography (LORETA) as underlying the acute changes observed in the EEG.

4. The acute administration of *ayahuasca* would disrupt sensory and sensorimotor gating.

5. Oral administration of *ayahuasca* would lead to measurable plasma levels of the major alkaloids present in the tea, i.e., DMT, harmine, harmaline and *d*-tetrahydroharmine.

6. The in vivo inhibition of MAO elicited by the β-carbolines present in *ayahuasca* could be measured by determining the levels of neurotransmitter metabolites in urine. *Ayahuasca* administration should lead to decreases in the excretion of MAO-dependent metabolites and to increases in COMT-dependent metabolites.

7. The acute administration of *ayahuasca* would induce elevations in blood pressure and heart rate. No hypotheses were postulated regarding other somatic-dysphoric or adverse events associated to *ayahuasca* administration.

AIMS OF THE STUDY

The present investigation aimed to obtain information on the human pharmacology of *ayahuasca*. The study focussed on the effects of *ayahuasca* following its acute administration in a controlled clinical trial, i.e., incorporating a placebo and a double-blind randomized design, without addressing at this stage any possible adverse psychopathological effects derived from repeated consumption, or studying any hypothetical therapeutic properties of the tea.

Specific main objectives:

1. Measure the nature and time course of subjective effects elicited by acute *ayahuasca* administration.

2. Assess the CNS effects of *ayahuasca* by means of quantitative pharmaco-electroencephalography (q-EEG).

3. Conduct an exploratory analysis of the brain cortical regions responsible for the observed q-EEG effects by means of Low Resolution Electromagnetic Tomography (LORETA).

4. Measure the effects of *ayahuasca* on sensory and sensorimotor gating.

5. Describe the pharmacokinetics of DMT and the β-carbolines present in *ayahuasca*, after the oral administration of various doses of the preparation.

6. Measure *in vivo* the inhibition of MAO provoked by acute *ayahuasca* administration.

7. Assess the general tolerability of *ayahuasca*, i.e., the subject's vital signs after the drug's administration, and any event, either physical or psychological, regarded as unpleasant by the subject. Additionally, evaluate hematological and biochemical parameters.

Specific secondary objectives:

1. Translate into Spanish and explore the sensitivity and psychometric properties, i.e., reliability and construct validity of a recently developed self-report instrument designed to evaluate the subjective effects elicited by psychedelics: the Hallucinogen Rating Scale (HRS).

2. Develop and validate an analytical methodology to adequately quantify *ayahuasca* alkaloids in plasma in order to characterize their pharmacokinetics in humans following oral administration of the tea.

SUMMARY OF THE EXPERIMENTAL DESIGN

The steps taken in the course of the present project are described below in chronological order. First, the Spanish version of the HRS questionnaire was administered both to *ayahuasca* users and to users of psychedelics in order to explore the psychometric properties of this instrument. The next stage was the initiation of the clinical studies with a pilot study conducted to explore the general tolerability, i.e., safety of the lyophilizate, and its capacity to elicit psychotropic effects. The information obtained was used to establish the doses to be administered in the larger final study. This involved a greater number of volunteers and study variables, and the implementing of an optimal design.

Questionnaire assessment studies

Study 1

Participants: 75 users of *ayahuasca*.

Design: Volunteers answered the HRS approximately 4 hours after intake (immediate retrospective assessment).

Variables: Cronbach's alpha.

Study 2

Participants: 56 polydrug users.

Design: Volunteers answered the HRS and the ARCI recalling effects of their last psychedelic drug intake (delayed retrospective assessment).

Variables: Cronbach's alpha and correlations between HRS and ARCI scales.

Results in: *Psychometric assessment of the Hallucinogen Rating Scale*.

Pilot Clinical Study

Participants: 6 male volunteers with prior experience with *ayahuasca*.

Design: Single-blind, placebo-controlled, crossover, increasing doses: 0.5, 0.75 and 1.0 mg DMT/kg body weight.

Variables: HRS, ARCI, verbal reports.

SBP, DBP, HR, hematological and biochemical parameters.

Results in: *Subjective effects and tolerability of the South American psychoactive beverage ayahuasca in healthy volunteers.*

Final Clinical Study

Participants: 18 volunteers (15 male, 3 female) with prior experience with psychedelic drug use.

Design: Double-blind, placebo-controlled, randomized, crossover: 0.6 and 0.85 mg DMT/kg body weight.

Variables: HRS, ARCI, APZ, verbal reports.

SBP, DBP, HR, hematological and biochemical parameters.

EEG (Topography and LORETA).

PPI, P50.

Pharmacokinetics.

Urine monoamine metabolite excretion.

Results in: *Human pharmacology of ayahuasca: subjective and cardiovascular effects, monoamine metabolite excretion and pharmacokinetics.*

Topographic pharmaco-EEG mapping of the effects of the South American psychoactive beverage ayahuasca in healthy volunteers.

Effects of ayahuasca on sensory and sensorimotor gating in humans as measured by P50 suppression and prepulse inhibition of the startle reflex, respectively.

Determination of N,N-dimethyltryptamine and β-carboline alkaloids in human plasma following oral administration of Ayahuasca.

Effects of the South American psychoactive beverage Ayahuasca on regional brain electrical activity in humans: a functional neuroimaging study using low resolution electromagnetic tomography (LORETA).

Estimation of the bioavailability of DMT in ayahuasca.

Abbreviations

SBP:	Systolic blood pressure
DBP:	Diastolic blood pressure
HR:	Heart rate
LORETA:	Low Resolution Electromagnetic Tomography
HRS:	Hallucinogen Rating Scale
ARCI:	Addiction Research Center Inventory
APZ:	Altered States of Consciousness Questionnaire
EEG:	Electroencephalography
PPI:	Prepulse inhibition of the startle reflex
P50:	Suppression of the P50 auditory evoked potential in a paired-stimuli paradigm

RESULTS

Original publications

Subjective effects and tolerability of the South American psychoactive beverage Ayahuasca in healthy volunteers.

Pscyhopharmacology 2001; 154:85-95.

Psychopharmacology (2001) 154:85–95
DOI 10.1007/s002130000606

ORIGINAL INVESTIGATION

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Subjective effects and tolerability of the South American psychoactive beverage *Ayahuasca* in healthy volunteers

Received: 4 July 2000 / Accepted: 3 October 2000 / Published online: 14 December 2000

Abstract *Rationale: Ayahuasca* is a South American psychoactive beverage that contains the naturally occurring psychedelic agent *N*,*N*-dimethyltryptamine (DMT). This "tea" has been used for centuries in religious and medicinal contexts in the rain forest areas of South America and is presently gaining the attention of psychedelic users in North America and Europe. *Objectives:* In the present study, the psychological effects and tolerability of *ayahuasca* were assessed. *Methods:* Three increasing doses of encapsulated freeze-dried *ayahuasca* (0.5, 0.75, and 1.0 mg DMT/kg body weight) were administered to six healthy male volunteers with prior experience in the use of this tea, in a single-blind crossover placebo-controlled clinical trial. *Results: Ayahuasca* produced significant dose-dependent increases in five of the six subscales of the Hallucinogen Rating Scale, in the LSD, MBG, and A scales of the Addiction Research Center Inventory, and in the "liking", "good effects" and "high" visual analogue scales. Psychological effects were first noted after 30–60 min, peaked between 60–120 min, and were resolved by 240 min. The tea was well tolerated from a cardiovascular point of view, with a trend toward increase for systolic blood pressure. Modified physical sensations and nausea were the most frequently reported somatic-dysphoric effects. The overall experience was regarded as pleasant and satisfactory by five of the six volunteers, while one volunteer experienced an intensely dysphoric reaction with transient disorientation and anxiety at the medium dose and voluntarily withdrew from the study. *Conclusions: Ayahuasca* can be described as inducing changes in the perceptual, affective, cognitive, and somatic spheres, with a combination of stimulatory and visual psychoactive effects of longer duration and milder intensity than those previously reported for intravenously administered DMT.

Keywords *Ayahuasca* · DMT · Subjective effect · Tolerability · Human

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Introduction

Ayahuasca, a potent psychotropic drink that has been used for centuries for magico-religious purposes and folk medicine in the Amazon and Orinoco river basins (Dobkin de Ríos 1972; Schultes and Hofmann 1982), is becoming increasingly popular in Europe and North America as a sacramental drug (Metzner 1999). In recent years, the use of *ayahuasca* has spread outside South America, and several groups using this tea have become established in Spain and other European countries (Marshall 1997; López 1999), where the tea is reportedly used to facilitate self-knowledge and introspection. A relevant facet in expanding *ayahuasca* use can be attributed to the growing interest of the many individuals who are interested in shamanic practices, in addition to the activities of a number of Brazilian syncretic religions, particularly the *Santo Daime* and the *União do Vegetal*, that have combined Old World religious beliefs with the indigenous use of *ayahuasca*. Because this tea contains measurable amounts of *N*,*N*-dimethyltryptamine (DMT), the *ayahuasca* churches are actively working to obtain legal exemption for *ayahuasca* use within a religious context outside Brazil, the only country where it currently enjoys legal protection, analogous to the status held

by the Native American Church for the use of *peyote* (*Lophophora williamsii*, a mescaline-containing cactus) in the United States. Even though the number of users is still relatively small outside of Brazil, *ayahuasca* use has raised concerns for public health (Callaway and Grob 1998), and extensive clinical data on its somatic, psychological, and neurophysiological effects are indicated.

Ayahuasca, also known as *Daime* or *Hoasca* in Brazil, *Yajé* in Colombia, or *Natem* in Ecuador, is generally obtained by infusing the shredded stalk of the malpighiaceous vine *Banisteriopsis caapi* with the leaves of *Psychotria viridis* (Rubiaceae) or *Diplopterys cabrerana* (Malpighiaceae). *B. caapi* contributes a mixture of β-carboline alkaloids to the tea, particularly harmine, tetrahydroharmine (THH), and trace amounts of harmaline (Rivier and Lindgren 1972). *P. viridis* and *D. cabrerana* are rich in the psychedelic indole DMT (River and Lindgren 1972; Schultes and Hofmann 1980; Callaway et al. 1996).

DMT, the main psychotropic agent of *ayahuasca*, is capable of eliciting an intensely emotional dream-like experience characterized by vivid visual imagery, perceptual and cognitive changes, and profound modifications in the sense of self and reality, when administered parenterally (Strassman et al. 1994). On the molecular level, DMT has affinity for 5-HT_2 and 5-HT_{1A} binding sites, similarly to LSD (Pierce and Peroutka 1989; Deliganis et al. 1991), and is structurally similar to serotonin. Interestingly, DMT is known for its lack of psychoactivity when orally ingested, even in quantities in the order of grams (Ott 1999), due to metabolism by monoamine oxidase (MAO; Suzuki et al. 1981). The β-carbolines present in *ayahuasca*, particularly harmine and harmaline, have been found to inhibit MAO (McKenna et al. 1984), an effect that apparently allows the viable access of DMT to the systemic circulation and the central nervous system. In addition to the action of DMT on serotonin receptors, it has also been suggested that *ayahuasca*'s psychoactive effects may also be partly due to a general increase of catecholamines and serotonin (Callaway et al. 1999). This increase would be due to both the inhibited metabolic breakdown of serotonin in addition to its uptake inhibition by THH and also competition with DMT for receptor sites (Callaway et al. 1999). Thus, *ayahuasca* constitutes a very complex psychoactive preparation, acting at least through three different pharmacologic mechanisms.

In the present paper we report a single-blind placebo-controlled clinical trial conducted with *ayahuasca*, in which the subjective effects and tolerability of three different doses of *ayahuasca* were evaluated in healthy volunteers. This study is part of a wider research project designed to further characterize the pharmacologic effects of this tea.

Materials and methods

Volunteers

For ethical reasons, participation in this initial study was limited to six healthy male volunteers having previous experience with *ayahuasca*. Volunteers were contacted by word of mouth in the Barcelona area of Spain, and all had previous exposure to the "tea", but had no formal connections to any *ayahuasca* church. The volunteers were given a structured psychiatric interview (DSM-III-R) and completed the trait-anxiety scale from the state-trait anxiety inventory (Spielberger et al. 1970). Exclusion criteria included a present or past history of axis-I disorders and alcohol or other substance dependence, and high scores on trait anxiety. Following the psychiatric interview, participants underwent a complete physical examination that included a medical history, laboratory tests, ECG, and urinalysis. Mean age was 32.2 years (range: 26–44), mean weight 71.5 kg (range: 66–85), and mean height 174.3 cm (range 167–186). All volunteers had previous experience with cannabis, cocaine, psychedelics, and other illicit substances. Regarding their prior experience specifically with *ayahuasca*, volunteers 1 and 2 had previously consumed it on 10 occasions, volunteer 3 on about 60 occasions, volunteer 4 on 2 occasions, volunteer 5 on 6 occasions, and volunteer 6 on 30 occasions. The study was conducted in accordance with the Declarations of Helsinki and Tokyo concerning experimentation on humans, and was approved by the hospital's ethics committee and the Spanish Ministry of Health. The volunteers received detailed information on the nature of *ayahuasca*, the general psychological effects of psychedelics, and their possible adverse effects, as reported in the psychiatric literature. All volunteers gave their written informed consent to participate.

Drug

A 9.6 litre batch of *ayahuasca* (*Daime*) was obtained from CEFLURIS, a Brazilian-based religious organization related to the *Santo Daime* church. The tea had the appearance of a brown-reddish suspension with a characteristic bitter-sour taste and smell, and a markedly acidic pH (3.63). In order to mask the drug in the single-blind design and establish accurate dosings, the tea underwent a freeze-drying process that yielded 611 g of a yellowish powder, which was subsequently homogenized and analyzed for alkaloid contents by an HPLC method previously described in the literature (Callaway et al. 1996). One gram of freeze-dried material contained 8.33 mg DMT, 14.13 mg harmine, 0.96 mg harmaline, and 11.36 mg THH. Thus, the alkaloid concentrations in the original tea were as follows: DMT 0.53 mg/ml, harmine 0.90 mg/ml, harmaline 0.06 mg/ml, and THH 0.72 mg/ml. The DMT concentration found in the tea was similar to that reported previously for a sample of *Daime* (Liwszyc et al. 1992) and several Peruvian *ayahuasca* samples (McKenna et al. 1984), and twice as great as the amount reported for a sample of *Hoasca* from the Brazilian church *União do Vegetal* (Callaway et al. 1996). Similarly, the β-carboline concentrations found in the *ayahuasca* used in the present study were also higher than those reported in the previously mentioned samples. In view of the mild psychological effects reported from the 0.48 mg DMT/kg body weight dosage (Grob et al. 1996), and considering the total amounts of DMT consumed in what have been reported as typical doses (McKenna et al. 1984; Liwszyc et al. 1992), the following experimental doses were chosen for the present study: 0.5 mg DMT/kg body weight as the low dose and 0.75 and 1.0 mg DMT/kg body weight as the medium and high dose, respectively. The freeze-dried material was encapsulated in 00 gelatin capsules containing 0.5, 0.25, or 0.125 g, and stored at –20°C under nitrogen atmosphere and protected from light until administered to the volunteers. Placebo capsules consisted of 00 gelatin capsules with 0.75 g lactose. Each volunteer received his calculated individual dose by combination of these capsules. Placebo capsules were added when necessary, so that all volunteers received 20 capsules on each experimental day.

Study design and experimental procedure

The study was carried out in a single-blind fashion. Volunteers were informed that they would receive a single oral dose of encapsulated freeze-dried *ayahuasca* (one low, one medium, and one high dose) or placebo on each of 4 experimental days. In order to avoid subjective effects related to expectancy, the volunteers were also informed that administrations would be made in a double-blind balanced fashion. For security reasons, they were actually administered in increasing doses, i.e., placebo for the first session, the low dose containing 0.5 mg DMT/kg for the second session, the medium dose containing 0.75 mg DMT/kg for the third session, and the high dose containing 1.0 mg DMT/kg for the fourth and final session, in order to control for tolerability and the possible risk in elevations of cardiovascular parameters. Two weeks prior to the beginning of the experimental sessions, volunteers abstained from any medication or illicit drug and remained drug-free throughout the 4 study weeks. Urinalysis for illicit drug use was carried out for each experimental session. Additionally, volunteers abstained from alcohol, tobacco, and caffeinated drinks 24 h prior to each experimental day. Experimental days were a week apart.

The volunteers were admitted to the research unit on 4 separate experimental days. Upon arrival at 8:00 a.m. under fasting conditions, a urine sample was collected, a cannula was inserted in the cubital vein of their right arm for drawing blood samples, and capsules were administered by approximately 9:00 a.m. with 250 ml tap water. Throughout the experimental session the volunteers remained seated in a comfortable reclining chair in a quiet and dimly lit room. The experimenter remained beside the volunteer for most of the time, and no music was used during the sessions. Four hours after administration of the capsules, the volunteers left the room, answered subjective effect questionnaires, were able to have a light meal if they wished to, and were discharged after 5 h from the administration.

Measurements

Besides the measures described below, spontaneous verbally reported effects were also recorded. Additionally, blood samples were drawn at set time points in order to establish the alkaloids' pharmacokinetic profiles (not reported here). The time points selected for the measurements described below were based on field observations of duration of *ayahuasca* effects, and on the published pharmacokinetic and pharmacodynamic data by Callaway et al. (1999).

Psychological measures

The psychological effects elicited by *ayahuasca* were measured by means of visual analogue scales (VAS) and self-report questionnaires. VAS were 100-mm horizontal lines with the following labels: "any effect" indicated any effect, either physical or psychological, that the volunteer attributed to the administered dosage; "good effects" indicated any effect the volunteer valued as good; "liking" reflecting that the volunteer liked the effects of the administered substance; "drunken" indicating any dizziness or lightheadedness; "stimulated" indicating any increases in thought speed and/or content, or any increases in associations and/or insights; and "high" which reflected any positive psychological effect the volunteer attributed to the treatment. The volunteers were requested to answer the VAS immediately before administration and at 15, 30, 45, 60, 90, 120, 150, 180, 210, and 240 min after administration.

Self-report questionnaires included Spanish adaptations of the Hallucinogen Rating Scale (HRS) and the Addiction Research Center Inventory (ARCI). The HRS version, which had been previously translated from English and validated in Spanish (Riba et al. 2000), includes six subscales: "somaesthesia", reflecting somatic effects; "affect", sensitive to emotional and affective responses; "volition", indicating the volunteer's capacity to willfully interact with his/her "self" and/or the environment; "cognition", describing modifications in thought processes or content; "perception", measuring visual, auditory, gustatory, and olfactory experiences; and finally "intensity", which reflects the strength of the overall experience (Strassman et al. 1994). The ARCI (Lamas et al. 1994) consists of five scales or groups: morphine-benzedrine group (MBG), measuring euphoria; pentobarbital-chlorpromazine-alcohol group (PCAG), measuring sedation; lysergic acid diethylamide scale (LSD), measuring somatic-dysphoric effects; and the benzedrine group (BG) and the A scale, for amphetamine, both sensitive to stimulants. The volunteers answered the ARCI immediately before drug administration and, 4 h after drug intake, they again answered the ARCI and the HRS.

Tolerability measures

Cardiovascular variables were recorded by means of a sphygmomanometer cuff (Dinamap Critikon, Tampa, Fla., USA) which was placed around the volunteer's left arm. Blood pressure [systolic (SBP) and diastolic (DBP)] and heart rate were measured immediately before administration (baseline) and at 15, 30, 45, 60, 90, 120, 150, 180, 210, and 240 min after intake. Somatic-dysphoric effects were recorded by means of the questionnaires previously mentioned, and as spontaneous verbal reports. Finally, after each experimental session, a blood sample was taken for laboratory testing, which included blood cell counts, plasma bilirubin, creatinine, and liver enzymes.

Statistical analysis

Values from cardiovascular measures and ARCI scores were transformed to differences from baseline and differences from preadministration scores, respectively. Transformed values, HRS scores, and mean values obtained across time points for a given treatment (i.e., cardiovascular and VAS data) were analyzed by means of a non-parametric Friedman test. When a significant effect was observed, *post hoc* comparisons were performed using the Wilcoxon test. In all tests performed, differences were considered statistically significant for P values lower than 0.05.

Results

Psychological effects

Results for the statistical analyses performed on all subjective effect variables are presented in Table 1. A significant effect of treatment was observed for all seven VAS items, all HRS subscales except "volition", and the A, MBG, and LSD scales of the ARCI. The 0.5 mg DMT/kg body weight dosage chosen in the present study as the lower dose proved to be psychoactive in five of the six volunteers and subthreshold for the sixth volunteer, who mistook it for the placebo. At this dose, the Wilcoxon test showed significant effects for all VAS items except for "high". A significant effect was also found for the HRS "somaesthesia" subscale. Finally, the ARCI questionnaire showed a significant increase in the MBG scale.

When administered at 0.75 and 1.0 mg DMT/kg body weight, *ayahuasca* was correctly identified as an active substance by all participants. All VAS items and all HRS subscales, except for "volition", discriminated between each of these two doses and the placebo. At the medium

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Table 1 Statistical analyses performed on the visual analogue scale (VAS) scores (mean values across ten time points) and on scores obtained for the Hallucinogen Rating Scale (HRS) subscales and Addiction Research Center Inventory (ARCI) (differences from pre-drug values) (n=5). *NS* Not significant, *A* amphetamine scale, *LSD* lysergic acid diethylamide scale, *BG* benzedrine group, *MBG* morphine-benzedrine group, *PCAG* pentobarbital-chlorpromazine-alcohol group

Variable	Friedman test	Wilcoxon test					
		Placebo			0.5 mg/kg		0.75 mg/kg
	P value	0.5	0.75	1.0	0.75	1.0	1.0
VAS							
Any effect	**	*	*	*	*	*	NS
Good effects	**	*	*	*	(*)	*	NS
Visions	*	*	*	*	NS	(*)	NS
Liking	**	*	*	*	(*)	*	NS
Drunken	**	*	*	*	*	*	NS
Stimulated	**	*	*	*	(*)	NS	NS
High	**	(*)	*	*	*	*	NS
HRS							
Somaesthesia	**	*	*	*	*	NS	NS
Perception	*	NS	*	*	NS	(*)	NS
Cognition	*	NS	*	*	(*)	*	NS
Volition	NS	–	–	–	–	–	–
Affect	**	(*)	*	*	*	(*)	NS
Intensity	**	(*)	*	*	*	NS	NS
ARCI							
MBG	**	*	*	*	(*)	NS	NS
BG	NS	–	–	–	–	–	–
A	**	(*)	*	*	NS	(*)	NS
LSD	*	(*)	(*)	*	NS	NS	NS
PCAG	NS	–	–	–	–	–	–

*P<0.05, **P<0.01, (*)P<0.1

dose (i.e., 0.75 mg DMT/kg) the ARCI MBG and A scales showed statistically significant differences from the placebo. At the high dose, the LSD, MGB, and A scales showed significant differences from the placebo. Regarding discrimination between the doses, five of the seven VAS items and the HRS "cognition" subscale were able to discriminate between the low and the high doses. None of the variables were able to discriminate between the medium and the high doses. Three VAS items, "any effects", "drunken", and "high", were discriminative between the low and medium doses. Discrimination between these two doses was also achieved by the HRS "somaesthesia", "affect", and "intensity" subscales.

Scores on the HRS subscales for the four experimental conditions are shown in Fig. 1. Pre- and post-treatment scores on the ARCI scales for the four experimental conditions are shown in Fig. 2. The time course of effects, as reflected by the seven VAS items, is presented in Fig. 3. The initial somatic effects of *ayahuasca* appeared between 15–30 min, which translated as increases in the "any effect" VAS. This was followed by an onset of psychological effects at around 30–60 min, which was reflected by the increases in the other six VAS items. Both somatic and psychic effects peaked between 60 and 120 min after drug intake and gradually decreased to baseline levels at approximately 240 min. It is worth noting that the "good effects" and "liking" items of the VAS remained elevated at 240 min after drug administration, when most of the perceptual, cognitive, and affective effects had disappeared. The volunteers verbally described this state as a lingering sensation of well-being after the resolution of the more intense psychotropic effects.

Tolerability

Cardiovascular effects

Mean values for SBP, DBP, and heart rate over time are presented in Fig. 4 as differences from their baseline values. All three *ayahuasca* doses produced increases in SBP and DBP when compared with placebo. Changes were not statistically significant, although a robust trend toward significance was observed for SBP (P=0.0503) at the high dose. The peak differences in SBP were 13.8 mm Hg between the high dose and placebo, 13.4 mm Hg between the medium dose and placebo, and 8.8 mm Hg between the low dose and placebo. The maximal increases in SBP were observed at 90 min after administration of all three *ayahuasca* doses. The peak differences in DBP were 10.4 mm Hg between the high dose and placebo, 9.8 mm Hg between the medium dose and placebo, and 8.6 mm Hg between the low dose and placebo. The maximal increases in DBP were observed at 60 min after administration of all three *ayahuasca* doses. Mean arterial pressures showed a 10.6 mm Hg maximum difference from placebo at 60 min. Heart rate was affected very little by *ayahuasca*. Increases above baseline values were only seen for the medium and high doses, with peak differences of 9.2 beats/min between the high dose and placebo, 8 beats/min between the medium dose and placebo, and 6.4 beats/min between the low dose and placebo at 45 min after drug administration. At no point did SBP reach 140 mm Hg, nor did heart rate reach 100 beats/min for any individual volunteer. On the other hand, two volunteers showed sporadic

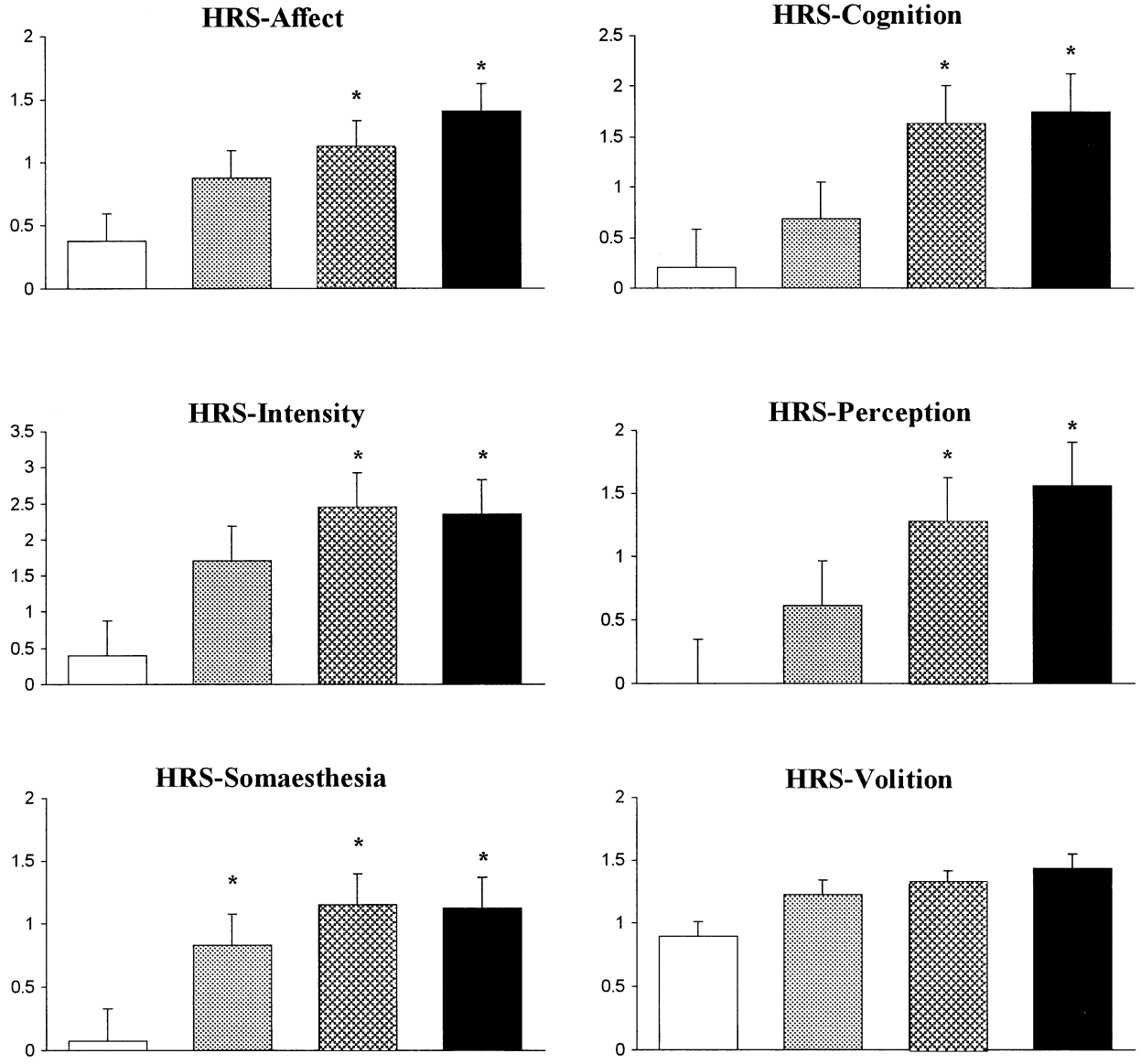

Fig. 1 Mean scores on the six Hallucinogen Rating Scale (HRS) subscales after administration of placebo (□), 0.5 mg *N*,*N*-dimethyltryptamine (DMT)/kg body weight *ayahuasca* (*lightly shaded*), 0.75 mg/kg (*shaded*), and 1.0 mg/kg (■). *Error bars* denote 1 standard error of mean (n=5). Significant differences from placebo (Wilcoxon test, P<0.05) are indicated by an *asterisk*

DBP values between 91–93 mm Hg after the medium and high doses, which lasted between 15 and 30 min.

Somatic-dysphoric effects

Table 2 lists the main somatic-dysphoric effects reported by the volunteers either spontaneously, or as positive responses to particular items in the HRS and ARCI questionnaires.

Blood analysis

No clinically relevant alterations were observed in the hematological or biochemical parameters tested after completion of each experimental session.

Verbal reports

The first effects noted by the volunteers were somatic modifications which included burning sensations in the stomach, tingling sensations, changes in perception of body temperature and skin sensitivity, and mild nausea. The onset of psychic effects was generally sudden and intense. Volunteers reported a certain degree of anxiety or fear at this initial stage, tending to decrease thereafter. Visual imagery was characteristic and dose-dependent. The images and visual modifications did not persist throughout the entire experience, but usually came and went in waves. These effects ranged from increases

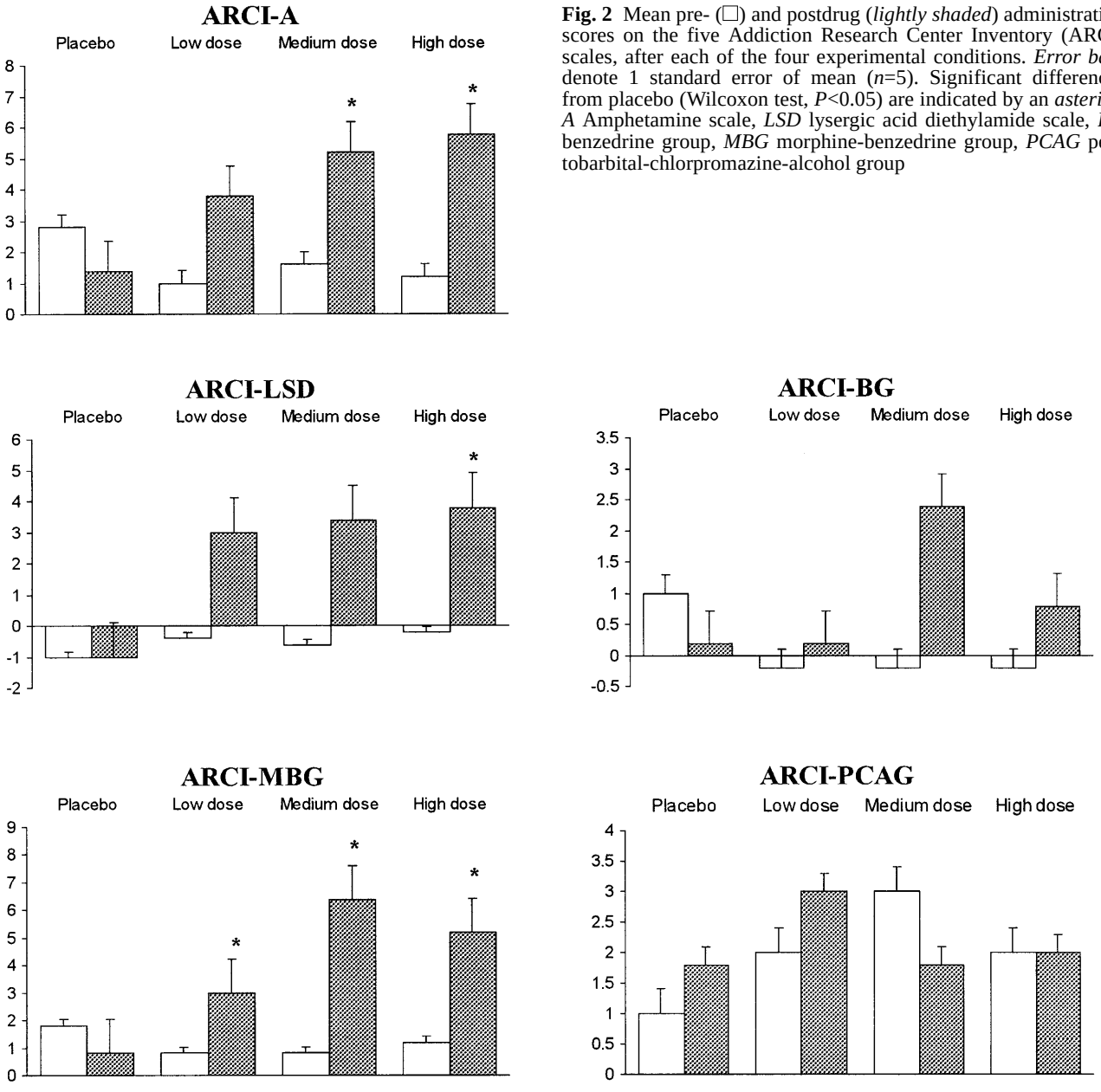

Fig. 2 Mean pre- (□) and postdrug (*lightly shaded*) administration scores on the five Addiction Research Center Inventory (ARCI) scales, after each of the four experimental conditions. *Error bars* denote 1 standard error of mean (n=5). Significant differences from placebo (Wilcoxon test, P<0.05) are indicated by an *asterisk*. *A* Amphetamine scale, *LSD* lysergic acid diethylamide scale, *BG* benzedrine group, *MBG* morphine-benzedrine group, *PCAG* pentobarbital-chlorpromazine-alcohol group

in an object's brightness and sharpness, or as vibrations in the visual field, to rapidly moving patterns, and scenes that were visible with eyes either closed or open at the medium and high doses. Changes in auditory perception were also reported and showed a dose-dependent effect. Hearing was perceived to be enhanced, with sounds becoming more clear and distinct. Although infrequent, transient auditory phenomena were reported in some subjects at the three doses. Thought processes were also modified, with the volunteers reporting an enhanced rate of thinking which generally centered on personal psychologic content. These thoughts were experienced as providing new insight into personal concerns. As the doses increased, emotional reactions were intensified, with the volunteers experiencing happiness, sadness, awe, amazement, and at times simultaneously contradictory feelings. At the medium and high doses, volunteers agreed on the similarity of the experience to dreaming. Memories were present, mostly related to recent personal matters. The sense of self and the passing of time were deeply affected at the medium and high doses. While sensations of closeness to others, happiness, and euphoria were similar at the medium and high doses, sensations of detachment from the body, oneness with the universe, and chaos, were more frequently reported with the latter. Five of the six volunteers were able to interact with the experimenter and the environment without major problems at all three doses. The sixth volunteer experienced a brief but intense disorientation state at the medium dosage. It is noteworthy that this volunteer had the least amount of experience with *ayahuasca*, having consumed it prior to the study on on-

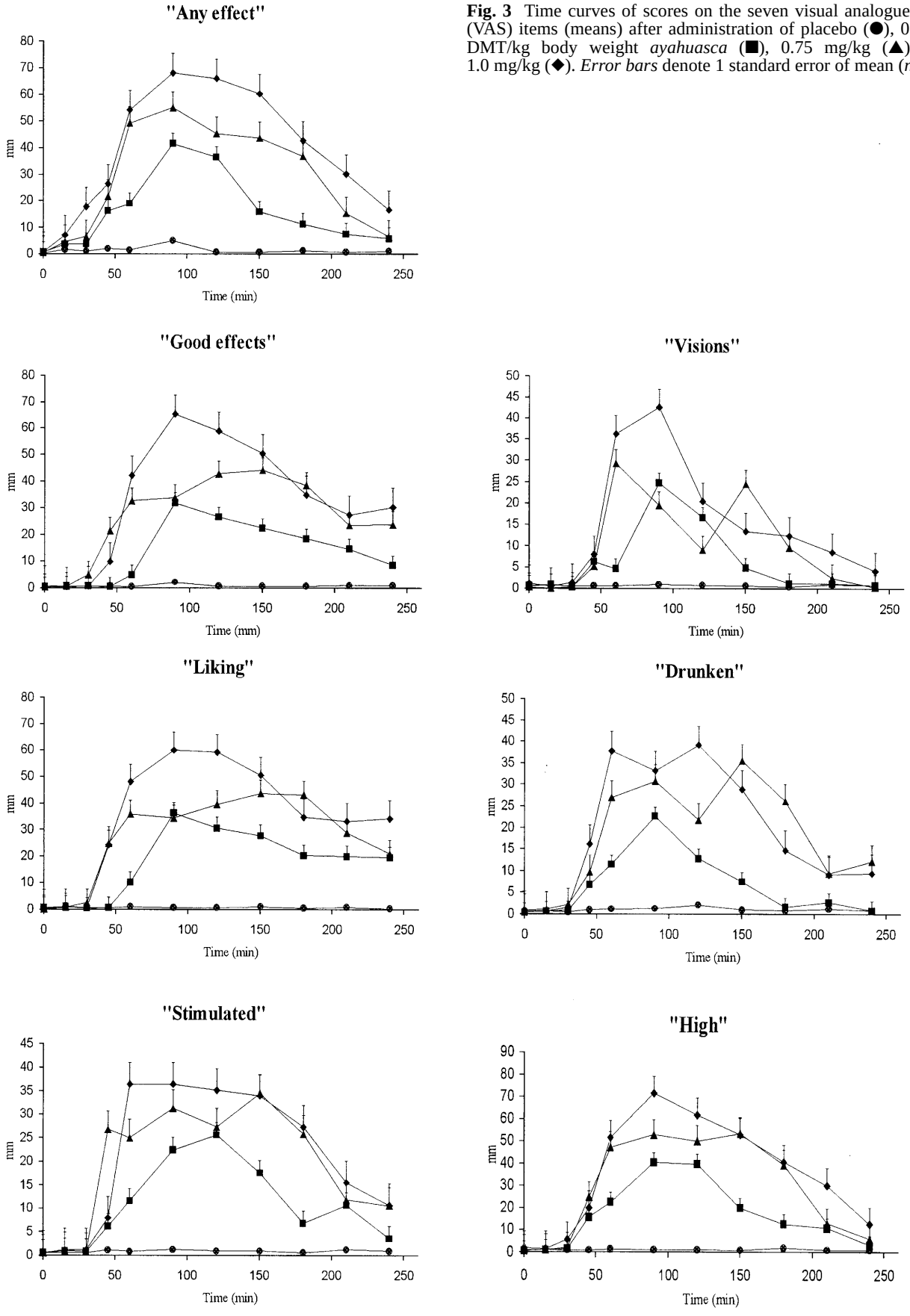

Fig. 3 Time curves of scores on the seven visual analogue scale (VAS) items (means) after administration of placebo (●), 0.5 mg DMT/kg body weight *ayahuasca* (■), 0.75 mg/kg (▲), and 1.0 mg/kg (◆). *Error bars* denote 1 standard error of mean (*n*=5)

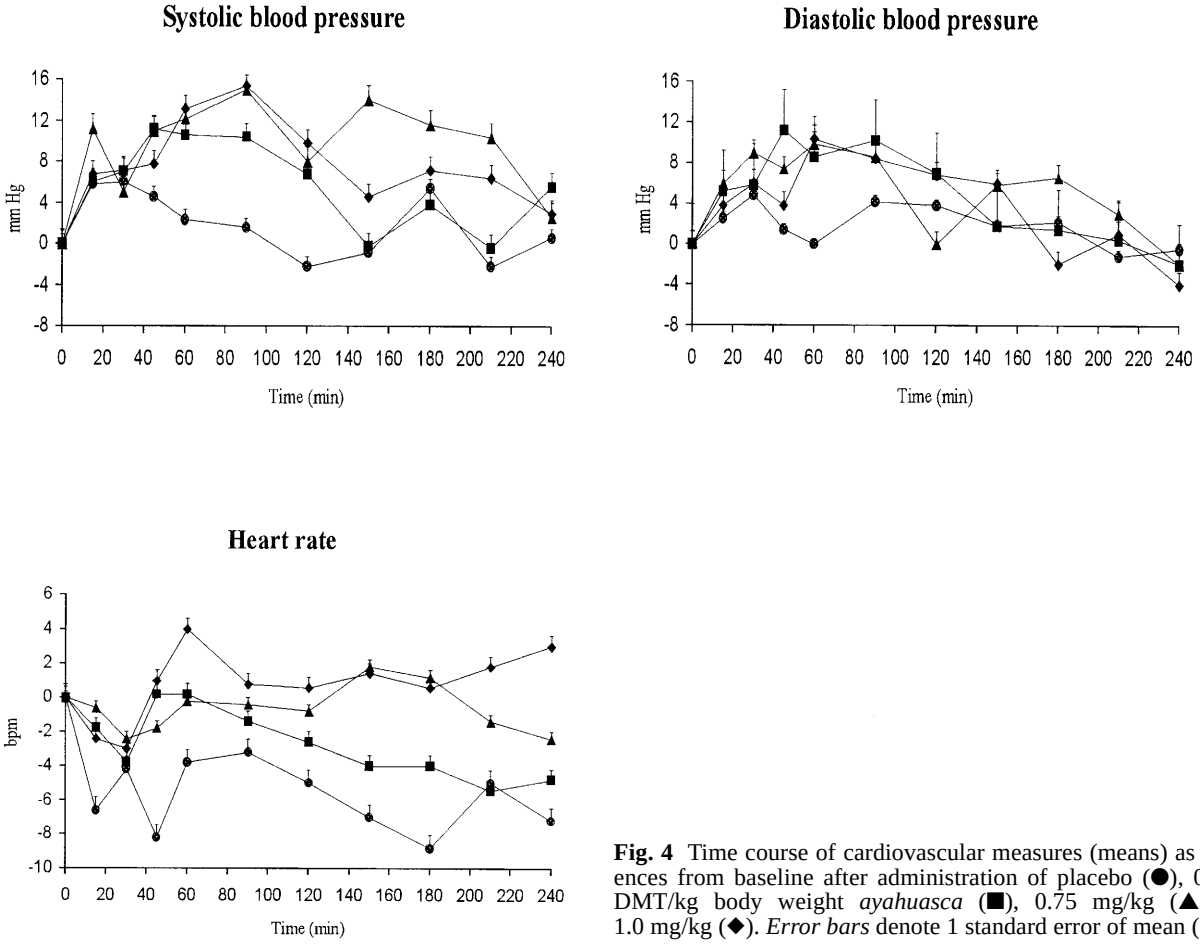

Fig. 4 Time course of cardiovascular measures (means) as differences from baseline after administration of placebo (●), 0.5 mg DMT/kg body weight *ayahuasca* (■), 0.75 mg/kg (▲), and 1.0 mg/kg (◆). *Error bars* denote 1 standard error of mean (n=5)

Table 2 Somatic-dysphoric effects spontaneously reported by the six volunteers, or as positive responses on particular items of the HRS and ARCI questionnaires on the 4 experimental days, presented as most to least frequently reported. Figures indicate the number of subjects who reported a specific effect, regardless of intensity, at the three different *ayahuasca* doses administered and placebo

	Somatic-dysphoric effect	Placebo	0.5 mg/kg	0.75 mg/kg	1.0 mg/kg
1	Body feels different[a]	1/6	5/6	6/6	5/5
2	Nausea[a]	0/6	4/6	5/6	3/5
3	Change in body temperature[a]	1/6	4/6	4/6	3/5
4	Electric/tingling feeling[a]	1/6	2/6	3/6	5/5
5	I have a disturbance in my stomach[b]	0/6	3/6	4/6	2/5
6	My hands feel clumsy[b]	1/6	2/6	3/6	3/5
7	My speech is slurred[b]	0/6	3/6	3/6	2/5
8	Urge to urinate[a]	1/6	1/6	3/6	3/5
9	Feel body shake/tremble[a]	0/6	1/6	3/6	2/5
10	Urge to move bowels[a]	0/6	2/6	0/6	3/5
11	I feel dizzy[b]	0/6	2/6	2/6	0/5
12	My head feels heavy[b]	0/6	2/6	2/6	0/5
13	Sweating[a]	0/6	1/6	2/6	1/5
14	A thrill has gone through me...[b]	0/6	0/6	1/6	0/5
15	Vomiting[c]	0/6	0/6	0/6	1/5
16	Disorientation[c]	0/6	0/6	1/6	0/5

[a]Item included in the HRS
[b]Item included in the ARCI
[c]Spontaneously reported

ly two occasions. Verbal support was sufficient to get him through this temporary crisis, but he was left with a general feeling of dissatisfaction toward the experience and withdrew from the study. Nevertheless, all volunteers, including this one, were well aware of the effects being caused by the administered drug and of their transient nature.

Discussion

The administration of *ayahuasca* to experienced healthy volunteers induced intense modifications of their conscious state, which was evaluated as dose-dependent elevations in all VAS items used, in five of the HRS subscales, and in the MBG, LSD, and A scales of the ARCI questionnaire. At no time of the study did any of the vol-

unteers lose consciousness or contact with reality. Compared with the effects of intravenous (IV) DMT (Strassman et al. 1994), clear differences were found in the intensity and duration of the experience. The slower onset and longer duration of effects seen for *ayahuasca* can be readily attributed to the oral route of administration for DMT and to the enzymatic blockade process (MAO inhibition) which mediates the drug's access to systemic circulation. Additionally, the competition between DMT and increasing levels of serotonin for available receptor sites may contribute to an overall attenuation of effects from *ayahuasca* vs IV administration of pure DMT. MAO inhibition not only allows for increased levels of serotonin and other monoamines but also temporarily blocks the immediate metabolism of DMT, thus extending its action relative to its IV administration. The cardiovascular effects observed were milder than those reported for IV DMT (Strassman and Qualls 1994). Peak increases of blood pressure and heart rate after *ayahuasca* were relatively delayed and comparable in magnitude to those brought about by a 0.1–0.2 mg/kg IV DMT dose. Our cardiovascular values are in line with those previously reported by Callaway and coworkers (1999) after an *ayahuasca* (*hoasca)* oral dose of 0.48 mg DMT/kg, though a direct comparison is not possible given the non placebo-controlled nature of this earlier study. Considering the fact that in the present study elevations were observed in cardiovascular parameter after placebo, it seems likely that the inclusion of a placebo control in the earlier study could have rendered lower increases of cardiovascular parameters for the 0.48 mg DMT/kg dose used. When compared with IV DMT, it is reasonable to assume that the reversible MAO-inhibiting properties of harmine and harmaline leads to a transient increase in endogenous monoamines, in addition to DMT's own cardiovascular effects. Nevertheless, the moderate nature of these increases could also be due to the simultaneous enhancement of vagal activity induced by decreased serotonin metabolism. Additionally, a*yahuasca* seemed to induce more somatic-dysphoric effects than IV DMT, the most frequently reported being the modifications in body feeling and nausea. These effects may be attributable to the β-carbolines present in the tea. A relationship between the nausea and other distressing effects on the digestive tract and increased 5-HT levels has been postulated (Callaway et al. 1999).

Scorings on the six HRS subscales and the nature of the effects elicited by *ayahuasca* at the present low dose resembled those reported by Strassman et al. (1994) after 0.1 mg/kg IV DMT. In both cases, somatic reactions predominated over perceptual or cognitive effects. Scores on the “affect”, “volition”, and “intensity” subscales were also close to those reported by Grob et al. (1996) after an *ayahuasca* dose equivalent to the low dose used in the present study. Except for the “perception” and “volition” subscales, which showed lower values, scores on the HRS at the medium dose were greater than those reported by Grob et al. (1996) and fell close to those described for 0.2 mg/kg IV DMT, a dosage known to be fully psychoactive for DMT (Strassman et al. 1994). These differences probably indicate less overwhelming perceptual effects and greater control over the experience after *ayahuasca*. Finally, the five volunteers who received the high dose (1.0 mg DMT/kg) identified it as being fully active and verbally described its effects as being very high in intensity. However, several subjective-effect variables showed a saturation relative to the 0.75 mg DMT/kg dose. This saturation, or ceiling effect, may indicate an “order” effect due to the exploratory nature of the study design, with doses being administered in an increasing order rather than in a randomized balanced manner. At the medium dose, scores on all HRS subscales were higher than those reported by Grob et al. (1996) in their single-dose study. The “cognition” subscale for the medium dose in the present study scored close to the value obtained by Strassman et al. (1994) at 0.4 mg/kg IV DMT, whereas scores on the other five subscales remained near those obtained after a 0.2 mg/kg IV DMT dose. Thus, not even at the 1.0 mg DMT/kg *ayahuasca* dose did the volunteers experience the overwhelming effects reported for the highest dose used in Strassman's study (0.4 mg/kg IV), probably reflecting the milder effects of DMT made orally active by means of MAO inhibition.

Results obtained for the ARCI-A scale are indicative of a subjective effect of increased activation. Despite the coexistence of marked somatic-dysphoric effects, as reflected by increases in the HRS-LSD scale, the administration of *ayahuasca* induced elevations in the ARCI-MBG scale, indicative of subjective feelings of well-being. The pleasant nature of the effects experienced by five of the six volunteers was also reflected as increases in the “good effects”, “liking”, and “high” VAS items, especially at the high dose. On the contrary, sedation ratings, as reflected by the ARCI-PCAG scale did not reach statistical significance and tended to decrease as the doses increased.

Regarding the similarities and differences of the *ayahuasca* experience with those elicited by other better characterized serotonergic psychedelics, important differences can be found in the time course of effects. A*yahuasca* effects are comparable in duration to those of psilocybin. On the other hand, mescaline and LSD are clearly longer-acting drugs, with peak effects at 3–5 h and an overall duration which can exceed 8 h (Strassman 1994). Psychological effects are difficult to compare between studies, due to the different psychometric instruments used. However, in a recent human study where the HRS was administered, psilocybin was found to induce increases in all the HRS subscales, including “volition”. This greater impairment of the subjects' capacity to interact with themselves and their surroundings was further corroborated by their verbal reports, which described sensations of loss of control and paranoid thoughts (Gouzoulis-Mayfrank et al. 1999a), neither of which were observed in the present study.

From a neurochemical perspective, data from preclinical studies strongly support the involvement of seroto-

nergic neurotransmission in the effects elicited by the classic psychedelics, which includes DMT. Such compounds containing an indole moiety bind with high affinity to both the 5-HT_{2A} and 5-HT_{1A} sites in the human brain. A close correlation has been found between psychotropic potency and binding at the 5-HT_{2A} site (Glennon et al. 1984) which is considered to be chiefly responsible for the behavioral effects elicited by these agents. The interaction with the 5-HT_{1A} site has recently been argued to modulate the intensity of the psychedelic experience (Strassman 1996). Additionally, evidence of a possible long-term modulation of serotonergic neurotransmission by *ayahuasca* has been reported in a previous study, in which an apparent upregulation of the platelet serotonin transporter was found in regular users of the tea (Callaway et al. 1994). Nevertheless, the role of dopaminergic involvement in the effects of the classic psychedelics has also been examined. A recent PET study found that the administration of psilocybin to human volunteers leads to the displacement of ^{11}C-raclopride in the striatum, an effect that may reflect an increase in dopamine release (Vollenweider et al. 1999). This secondary pro-dopaminergic activity may not be, however, the key to the perceptual and cognitive modifications induced by these agents, as in another study psilocybin's subjective effects were found to be increased rather than reverted by the D_2 receptor antagonist, haloperidol, while they were effectively counteracted by ketanserin and risperidone (Vollenweider et al. 1998).

Neuroimaging studies have revealed patterns of increased metabolism throughout the brain, and more specifically in the prefrontal cortices, particularly in the right hemisphere, in healthy volunteers after dosing with psilocybin (Vollenweider et al. 1997; Gouzoulis-Mayfrank et al. 1999b) and mescaline (Hermle et al. 1992). In this respect, recent electrophysiological studies have shown that 5-HT_{2A} receptor activation by serotonin mediates an increase of excitatory postsynaptic potentials (EPSPs) and currents (EPSCs) in pyramidal neurons of the neocortex and transitional cortex (Aghajanian and Marek 1997), an effect involving glutamate release and which is most pronounced in the medial prefrontal cortex (Marek and Aghajanian 1998a, b). These findings suggest an excitatory action of the classic psychedelics on the human frontal and parietal cortices and in the primary auditory and visual areas, which show very high densities of 5-HT_{2A} sites (Pazos et al. 1987). This excitatory effect may account for the enhancement and modifications of auditory and visual perception described by the volunteers. An analogous excitatory action on the somatosensory and visual association areas, both showing high 5-HT_{2A} densities, may also play a role in the peculiar modifications of perception brought about by *ayahuasca*. Finally, the activation of the anterior cingulate cortex (ACC), an area also showing dense serotonergic innervation and 5-HT_{2A} sites, could contribute to the emotional overtones of the *ayahuasca* experience. A recent PET study has implicated the ACC in normal emotional awareness (Lane et al. 1998), and psilocybin administration leads to increases in metabolism in this area, where 5-HT_{2A}-mediated EPSPs/EPSCs have also been recorded (Aghajanian and Marek 1997).

To summarize, *ayahuasca* induced a modified state of awareness in which stimulatory and psychedelic effects were present, and increased in a dose-dependent manner. The volunteers experienced modifications in perception and thought processes, such as rapid succession of thoughts, visions, and recollections of recent events, frequently having a marked emotional content. *Ayahuasca* was safely administered to the volunteers in this study and its effects were regarded as pleasant and desirable, except for one volunteer who experienced a dysphoric state that was characterized by transient disorientation and anxiety. Nevertheless, this adverse reaction was most likely related to the limited previous experience of that volunteer with the tea. Finally, the nature of the experience produced by *ayahuasca* resembled that of IV DMT, though it was less overwhelming, of longer duration, and displayed a greater variety of somatic-dysphoric effects. Moderate actions on blood pressure and heart rate were found and no clinically relevant changes were observed in biochemical parameters after any of the experimental sessions. Future studies will include measures of sensorimotor gating and brain imaging techniques in larger volunteer groups, using a double-blind balanced design, in order to obtain additional information on the mechanisms underlying the central effects of *ayahuasca.*

Acknowledgements We would like to express our gratitude to Esther Martínez, Félix González, and José María Fábregas for their continued support and help in contacting the people at CEFLURIS in Brazil, and to the latter for agreeing to submit their *ayahuasca* (*Daime*) for evaluation in a clinical trial. Thanks are also due to Sylvie Cotxet and David Martínez for their assistance during data collection. Finally, we greatly acknowledge the assistance of Ignasi Gich for his helpful comments on data analysis and revision of the manuscript. This work was supported by grant IR-97/034/980 from the Institut de Recerca HSCSP.

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J Pharmacol Exp Ther 2003; 306:73-83.

0022-3565/03/3061-73–83$7.00
THE JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS
Vol. 306, No. 1
49882/1069698
Printed in U.S.A.

JPET 306:73–83, 2003

Human Pharmacology of Ayahuasca: Subjective and Cardiovascular Effects, Monoamine Metabolite Excretion, and Pharmacokinetics

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Received February 3, 2003; accepted March 13, 2003

ABSTRACT

The effects of the South American psychotropic beverage ayahuasca on subjective and cardiovascular variables and urine monoamine metabolite excretion were evaluated, together with the drug's pharmacokinetic profile, in a double-blind placebo-controlled clinical trial. This pharmacologically complex tea, commonly obtained from *Banisteriopsis caapi* and *Psychotria viridis*, combines *N,N*-dimethyltryptamine (DMT), an orally labile psychedelic agent showing 5-hydroxytryptamine$_{2A}$ agonist activity, with monoamine oxidase (MAO)-inhibiting β-carboline alkaloids (harmine, harmaline, and tetrahydroharmine). Eighteen volunteers with prior experience in the use of psychedelics received single oral doses of encapsulated freeze-dried ayahuasca (0.6 and 0.85 mg of DMT/kg of body weight) and placebo. Ayahuasca produced significant subjective effects, peaking between 1.5 and 2 h, involving perceptual modifications and increases in ratings of positive mood and activation. Diastolic blood pressure showed a significant increase at the high dose (9 mm Hg at 75 min), whereas systolic blood pressure and heart rate were moderately and nonsignificantly increased. C_{max} values for DMT after the low and high ayahuasca doses were 12.14 ng/ml and 17.44 ng/ml, respectively. T_{max} (median) was observed at 1.5 h after both doses. The T_{max} for DMT coincided with the peak of subjective effects. Drug administration increased urinary normetanephrine excretion, but, contrary to the typical MAO-inhibitor effect profile, deaminated monoamine metabolite levels were not decreased. This and the negligible harmine plasma levels found suggest a predominantly peripheral (gastrointestinal and liver) site of action for harmine. MAO inhibition at this level would suffice to prevent first-pass metabolism of DMT and allow its access to systemic circulation and the central nervous system.

Ayahuasca, also known by the names Daime, Yajé, Natema, and Vegetal, is a psychotropic plant tea used by shamans throughout the Amazon Basin in traditional medicine, rites of passage, and magico-religious practices (Schultes and Hofmann, 1982; Dobkin de Rios, 1984). This ancient pattern of use has given way to a more widespread and frequent consumption by members of a number of modern Brazilian-based syncretic religious groups, mainly the Santo Daime and the Uniao do Vegetal, which have incorporated the use of the beverage in their rituals (Dobkin de Rios, 1996). In recent years, groups of followers of these Brazilian religions have become established in the United States and in several European countries, including Germany, Great Britain, Holland, France, and Spain (Anonymous, 2000). As a larger number of people have come into contact with ayahuasca, the tea has begun to attract the attention of biomedical researchers (Callaway et al., 1999; Riba et al., 2001b).

Ayahuasca is obtained by infusing the pounded stems of the malpighiaceous vine *Banisteriopsis caapi* either alone or, more frequently, in combination with the leaves of *Psychotria viridis* (rubiaceae) in Brazil, Peru, and Ecuador or *Diplopterys cabrerana* (malpighiaceae), used mainly in Ecuador and Colombia (Schultes and Hofmann, 1980; McKenna et al., 1984). *P. viridis* and *D. cabrerana* are rich in the psychedelic indole *N,N*-dimethyltryptamine (DMT; Rivier and Lindgren, 1972; Schultes and Hofmann, 1980), whereas *B. caapi* contains substantial amounts of β-carboline alkaloids, mainly harmine and tetrahydroharmine (THH), and to a lesser extent harmaline and traces of harmol and harmalol (Rivier and Lindgren, 1972; McKenna et al., 1984).

Article, publication date, and citation information can be found at http://jpet.aspetjournals.org.
DOI: 10.1124/jpet.103.049882.

ABBREVIATIONS: DMT, *N,N*-dimethyltryptamine; THH, tetrahydroharmine; LSD, D-lysergic acid diethylamide; CNS, central nervous system; MAO, monoamine oxidase; COMT, catechol-*O*-methyltransferase; VMA, vanillylmandelic acid; HVA, homovanillic acid; 5-HIAA, 5-hydroxyindoleacetic acid; MDMA, methylenedioxymethamphetamine; HPLC, high-performance liquid chromatography; VAS, visual analog scale(s); HRS, Hallucinogen Rating Scale; ARCI, Addiction Research Center Inventory; MBG, morphine-benzedrine group; PCAG, pentobarbital-chlorpromazine-alcohol group; BG, benzedrine group; AUC, area under the concentration-time curve; CL/F, total plasma clearance; V_z/F, apparent volume of distribution; ANOVA, analysis of variance; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate.

DMT is structurally related to the neurotransmitter serotonin and, like better-characterized psychedelics such as LSD and mescaline, binds to 5-hydroxytryptamine $_{2A}$ receptors in the central nervous system (CNS), where it acts as an agonist (Pierce and Peroutka, 1989; Smith et al., 1998). Studies in humans have shown that when administered parenterally, DMT provokes dramatic modifications in perception, the sense of self and reality that can be very intense but relatively short in duration (Strassman et al., 1994). The drug also exerts marked autonomic effects elevating blood pressure, heart rate, and rectal temperature, and causes mydriasis (Strassman and Qualls, 1994). Unlike the vast majority of known psychedelic phenethylamines, tryptamines, and ergolines, DMT is orally inactive (Ott, 1999), apparently due to metabolism by monoamine oxidase (MAO; Suzuki et al., 1981). Interestingly, harmine and harmaline, and, to a lesser extent, THH, are potent MAO inhibitors (Buckholtz and Boggan, 1977; McKenna et al., 1984). In 1968, Agurell and coworkers (cited in Ott, 1999, p. 172) postulated that the interaction between β-carbolines and DMT in ayahuasca "might result in specific pharmacological effects". It is now a widely accepted hypothesis that following ayahuasca ingestion, MAO inhibition brought about by harmine, given that it is more potent than THH and is present in the tea in larger amounts than harmaline (McKenna et al., 1984), prevents the enzymatic degradation of DMT, allowing its absorption. It has also been speculated that β-carbolines may contribute to the overall central effects of ayahuasca by blocking brain MAO and weakly inhibiting serotonin reuptake, which combined would lead to enhanced neurotransmitter levels and modulate the effects of DMT (Callaway et al., 1999).

In the present paper we report a double-blind placebo-controlled crossover clinical trial conducted with ayahuasca, in which subjective and cardiovascular effects, and alkaloid pharmacokinetics were assessed in a group of healthy volunteers experienced in psychedelic drug use. Additionally, urine monoamine metabolites were studied to measure in vivo the MAO-inhibitory effects of ayahuasca. In this respect, the neurotransmitters norepinephrine, epinephrine, and dopamine are physiologically degraded by MAO and catechol-*O*-methyltransferase (COMT) to produce deaminated and methylated metabolites, respectively. Serotonin, on the other hand, is exclusively metabolized by MAO to produce a deaminated compound. In vivo and in vitro studies have shown that when MAO is pharmacologically inhibited, the levels of MAO-dependent deaminated metabolites decrease and those of COMT-dependent methylated metabolites increase. In humans, MAO inhibitors decrease, after acute administration, the urinary excretion of vanillylmandelic acid (VMA), homovanillic acid (HVA), and 5-hydroxyindoleacetic acid (5-HIAA), the deaminated metabolites of norepinephrine/epinephrine, dopamine, and serotonin, respectively, while increasing that of metanephrine and normetanephrine, the methylated metabolites of epinephrine and norepinephrine, respectively (Pletscher, 1966; Koulu et al., 1989). Monoamine metabolites have both a CNS and a non-CNS origin, and their assessment in urine does not give information regarding the organ in which MAO was inhibited. Nevertheless, this approach can identify dose-response relationships after drug administration and allows for the study of the time course of MAO inhibition.

Materials and Methods

Volunteers

A total of 18 volunteers (15 males and 3 females) with experience in psychedelic drug use were recruited by word of mouth. Eligibility criteria required prior use of psychedelics on at least five occasions without sequelae derived thereof, i.e., psychedelic-related disorders as described in the DSM-III-R. Participants had used psychedelics from six to hundreds of times. The most commonly used psychedelic was LSD (17 of 18), followed by psilocybian mushrooms (15 of 18) and ketamine (10 of 18). The least commonly used were peyote (3 of 18), *Salvia divinorum* (3 of 18), mescaline (2 of 18), *Amanita muscaria* (2 of 18), and *Datura stramonium* (1 of 18). Although prior exposure to ayahuasca was not required for participation, two of the volunteers had ingested this tea before inclusion. Besides psychedelics, volunteers had consumed cannabis (18 of 18), cocaine (17 of 18), and MDMA (17 of 18). Volunteers were in good health, confirmed by medical history, laboratory tests, ECG, and urinalysis. Prior to physical examination, volunteers were interviewed by a psychiatrist (structured interview for DSM-III-R) and completed the trait-anxiety scale from the State-Trait Anxiety Inventory (Spielberger et al., 1970). Exclusion criteria included current or previous history of psychiatric disorder and/or family history of Axis-I psychiatric disorder in first degree relatives, alcohol or other substance dependence, and high scores on trait anxiety (over 1 standard deviation above normative mean). Participants had a mean age of 25.7 years (range 19–38), mean weight 66.47 kg (range 50.7–79.5), and mean height 175.11 cm (range 158–188). The study was conducted in accordance with the Declarations of Helsinki and Tokyo concerning experimentation on humans, and was approved by the hospital's ethics committee and the Spanish Ministry of Health. The volunteers received detailed information on the nature of ayahuasca, and the general psychological effects of psychedelics and their possible adverse effects, as reported in the psychiatric literature. All volunteers gave their written informed consent to participate.

Drug

To administer ayahuasca in accurate dosings and masked in a double-blind, double-dummy design, a 9.6-liter batch of Brazilian Daime was subjected to a freeze-drying process that yielded 611 g of powder, which was subsequently homogenized and analyzed. The DMT content was determined by HPLC, as described by Callaway et al. (1996), and the β-carbolines were determined according to a modified version of the method described therein. One gram of freeze-dried material contained 8.33 mg of DMT, 14.13 mg of harmine, 0.96 mg of harmaline, and 11.36 mg of THH, which corresponded to the following alkaloid concentrations in the original tea: DMT, 0.53 mg/ml; harmine, 0.90 mg/ml; harmaline, 0.06 mg/ml; and THH, 0.72 mg/ml. The ayahuasca doses administered to the volunteers in the present study were chosen based on tolerability and subjective effect data gathered in a previous study (Riba et al., 2001b). The low and the high dose contained, per kilogram of body weight: 0.6/0.85 mg of DMT, 1.0/1.4 mg of harmine, 0.07/0.09 mg of harmaline, and 0.82/1.16 mg of THH. The average (range) alkaloid content in milligrams administered in each dose (low dose/high dose) was: 39.8 (30.4–47.9)/57.4 (43.7–67.7) for DMT, 67.4 (51.6–81.2)/95.8 (74.2–114.8) for harmine, 4.6 (3.5–5.5)/6.5 (5.0–7.8) for harmaline, and 54.2 (41.5–65.3)/77.0 (59.6–92.3) for THH. The calculated individual dose for each volunteer was administered by combining 00 gelatin capsules containing different amounts of freeze-dried ayahuasca, i.e., 0.5 g, 0.25 g, or 0.125 g, and placebo capsules containing 0.75 g of lactose. Placebo capsules were added when necessary, so that all volunteers took the same number of capsules on each experimental day. It is interesting to note that although the amount of DMT administered with the present low dose was similar to that administered in the only other published study on the human pharmacology of ayahuasca (Callaway et al., 1999), the amounts of β-car-

bolines administered in this work were much lower. This was due to the different alkaloid proportions present in the tea samples used in each study. Thus, the average amounts (range) in milligrams administered by Callaway et al. (1999) were: 35.5 (28.8–43.2) for DMT, 252.3 (204.0–306.0) for harmine, 29.7 (24.0–36.0) for harmaline, and 158.8 (128.4–196.6) for THH.

Study Design

Each volunteer participated in four experimental sessions at least 1 week apart. Volunteers were informed that on each experimental day they would randomly receive a single oral dose of encapsulated freeze-dried ayahuasca (one low and one high dose), a placebo, and a random repetition of one of the three mentioned treatments. In actual fact, they all received a placebo on the first experimental day in a single-blind fashion, followed by one of the three treatments from days 2 to 4 in a double-blind balanced fashion, according to a randomization table. The first nonrandomized placebo was administered to familiarize the volunteers with the experimental setting and to minimize the stress associated with the experimental interventions. Volunteers were requested to abstain from any medication or illicit drug use 2 weeks before the beginning of the experimental sessions until the completion of the study. Volunteers also abstained from alcohol, tobacco, and caffeinated drinks 24 h before each experimental day. Urinalysis for illicit drug use was performed for each experimental session. The volunteers were admitted to the research unit on four separate experimental days. Upon arrival at 8:00 AM under fasting conditions, a cannula was inserted in the cubital vein of their right arm for drawing blood samples, and capsules were administered at approximately 10:00 AM with 250 ml of tap water. Throughout the experimental session, the volunteers remained seated in a comfortable reclining chair in a quiet, dimly lit room. At 4 h after administration of the capsules, when the most prominent subjective effects associated with the drug had disappeared, the volunteers had a meal. The last experimental time point was at 8 h, and volunteers were discharged approximately 9 h after administration.

Study Methods

Subjective Effect Measures. The subjective effects elicited by ayahuasca were measured by means of visual analog scales (VAS) and self-report questionnaires. VAS were 100-mm horizontal lines with the following labels: "any effect," indicating any effect, either physical or psychological, that the volunteer attributed to the administered drug; "good effects," indicating any effect the volunteer valued as good; "liking," reflecting that the volunteer liked the effects of the administered substance; "drunken," indicating any dizziness or lightheadedness; "stimulated," indicating any increases in thought speed and/or content, or any increases in associations and/or insights; "visions," indicating modifications in visual perception, including any variations in object shape, brightness, or color and any illusion, abstract or elaborate, seen with either eyes closed or open; and "high," which reflected any positive psychological effect the volunteer attributed to the drug. Except for the "visions" item, the other VAS items administered had been used in human studies by other researchers assessing the subjective effects of a variety of psychoactive drugs (Farré et al., 1993, 1998; Camí et al., 2000). The volunteers were requested to answer the VAS immediately before administration (baseline) and at 15, 30, 45, 60, and 75 min, and 1.5, 2, 2.5, 3, 3.5, 4, 6, and 8 h after administration.

Self-report questionnaires included the Hallucinogen Rating Scale (HRS) and the Addiction Research Center Inventory (ARCI). The HRS (Strassman et al., 1994) measures psychedelic-induced subjective effects and includes six scales: Somaesthesia, reflecting somatic effects; Affect, sensitive to emotional and affective responses; Volition, indicating the volunteer's capacity to willfully interact with his/her "self" and/or the environment; Cognition, describing modifications in thought processes or content; Perception, measuring visual, auditory, gustatory, and olfactory experiences; and, finally, Intensity, which reflects the strength of the overall experience. In the present study, a Spanish adaptation of the questionnaire was used (Riba et al., 2001a). The range of scores for all HRS scales is 0 to 4. The short version of the ARCI (Martin et al., 1971) consists of five scales or groups: MBG, morphine-benzedrine group, measuring euphoria and positive mood; PCAG, pentobarbital-chlorpromazine-alcohol group, measuring sedation; LSD, lysergic acid diethylamide scale, measuring somatic-dysphoric effects; BG, the benzedrine group, measuring intellectual energy and efficiency; and the A scale, an empirically derived scale measuring amphetamine-like effects. Both the A and BG scales are sensitive to psychostimulants. The range of scores is 0 to 16 for MBG, −4 to 11 for PCAG, −4 to 10 for LSD, −4 to 9 for BG, and 0 to 11 for A. The questionnaire had been translated into Spanish and validated by Lamas et al. (1994). Volunteers answered the ARCI immediately before drug administration and 4 h after drug intake, whereas the HRS was only answered at 4 h postadministration.

Cardiovascular Measures. Systolic and diastolic blood pressure and heart rate were measured with the volunteer seated, immediately before administration (baseline), and at 15, 30, 45, 60, 75, 90, 120, 150, 180, 210, and 240 min after intake using a sphygmomanometer cuff (Dinamap; Critikon, Tampa, FL) placed around the volunteer's left arm. No measurements were made after 240 min, the time point when subjects had their meal and after which they were allowed to move and leave the room.

Urine Samples. Urine was collected in fractions of 0 to 8 h, 8 to 16 h, and 16 to 24 h in plastic containers with 3 ml of 6 N HCl and kept in the refrigerator during the 0- to 24-h collection period. Volunteers took home the two plastic containers corresponding to the 8- to 16-h and 16- to 24-h periods. Volume of each fraction was recorded and pH was adjusted to 2 to 4 with 6 N HCl, and two 50-ml aliquots were frozen at −20°C and stored at −80°C until analysis. The following monoamine metabolites, VMA, HVA, 5-HIAA, metanephrine, and normetanephrine were quantified by means of HPLC with coulometric detection following previously validated procedures (Soldin and Hill, 1980; Parker et al., 1986; Gamache et al., 1993). The limit of quantification was 3 mg/l for VMA, HVA, and 5-HIAA, 0.05 mg/l for metanephrine, and 0.10 mg/l for normetanephrine.

Blood Samples. Blood samples (10-ml EDTA tubes) were drawn at baseline, 30, 60, 90, 120, and 150 min, and 3, 4, 6, 8, and 24 h after administration for analysis of DMT, harmine, harmaline, and THH concentrations in plasma and those of the *O*-demethylated metabolites harmol and harmalol. Samples were centrifuged at 2000 rpm for 10 min at 4°C and plasma was immediately frozen at −20°C. The frozen plasma samples were stored at −80°C until analysis. DMT was quantified by gas chromatography with nitrogen-phosphorus detection and the β-carbolines by means of HPLC with fluorescence detection following previously reported methods (Yritia et al., 2002). The limit of quantification was 1.6 ng/ml for DMT, 0.5 ng/ml for harmine, 0.3 ng/ml for harmaline, 1.0 ng/ml for THH, and 0.3 ng/ml for harmol and harmalol. The intraday and interday coefficients of variation were lower than 10.9% and 13.4%, respectively, for all determined compounds.

Pharmacokinetic Analysis

After quantification of the different compounds in plasma, the following pharmacokinetic parameters were calculated using a noncompartmental approach by means of WinNonlin software (version 3.0; Pharsight, Mountain View, CA): maximum concentration (C_{max}), time taken to reach the maximum concentration (T_{max}), and area under the concentration-time curve from 0 to 8 h (AUC_{0-8h}), calculated by means of the trapezoidal rule. AUC was extrapolated to infinity ($AUC_{0-\infty}$) by addition of the residual area calculated by the last plasma concentration/terminal elimination rate constant. Terminal half-life ($t_{1/2\lambda z} = \ln 2/\lambda_z$) was obtained by linear regression analysis of the terminal log-linear portion of the plasma-concentration curve. Clearance (CL/F) was determined as dose/$AUC_{0-\infty}$. Appar-

ent volume of distribution (V_z/F) was calculated as dose/($\lambda_z \cdot AUC_{0-\infty}$). The $AUC_{0-\infty}$ normalized by dose ($AUC_{0-\infty}$/D) was also calculated. All data are expressed as mean ± S.D. except for T_{max}, where median and range are given.

Statistics

Prior to statistical analysis, ARCI scores were transformed to differences from preadministration values, and the following parameters were calculated for VAS items: peak effect (maximum absolute change from baseline values), time taken to reach the maximum effect (t_{max}), and the 8-h area under the curve (AUC_{0-8h}) of effect versus time calculated by the trapezoidal rule. For cardiovascular variables, peak effect (maximum absolute change from baseline values) and the 4-h area under the curve (AUC_{0-4h}) of effect versus time were calculated. The obtained parameters, transformed ARCI scores, and raw HRS scores were analyzed by means of a one-way repeated measures ANOVA with drug (placebo, ayahuasca low dose, ayahuasca high dose) as factor. When a significant effect was observed, post hoc comparisons were performed using Tukey's multiple comparisons test. The time course of subjective effects was explored using repeated measures two-way ANOVAs with drug and time (13 time points) as factors. When a drug by time interaction was significant, multiple comparisons were performed at each time point by means of Tukey's test.

Monoamine metabolite levels in urine were analyzed by means of a one-way repeated measures ANOVA with drug (placebo, ayahuasca low dose, ayahuasca high dose) as factor. When a significant effect was observed, post hoc comparisons were performed using Tukey's test. The time course of effects was explored using repeated measures two-way ANOVAs with drug and time (three time points) as factors. Pharmacokinetic parameter comparisons between doses were performed by means of Student's t test, except for T_{max}, which was compared by means of a nonparametric Wilcoxon test.

To explore possible differences in the time-to-peak of DMT plasma concentrations and time-to-peak of subjective effects (for each of the administered VAS), nonparametric Wilcoxon tests were performed comparing T_{max} for DMT and t_{max} for each VAS. These tests were performed for data obtained after each of the two administered ayahuasca doses. In all tests performed, differences were considered statistically significant for p values lower than 0.05.

Results

Subjective Effects. Subjective effects results are shown in Tables 1 and 2 and Figs. 1 and 2. Ayahuasca administration induced significant increases in all six HRS scales, both after the low and the high dose, except for Volition, which showed statistically significant differences from placebo only after the 0.85 mg of DMT/kg dose. The ARCI questionnaire showed statistically significant dose-dependent increases after ayahuasca in measures of stimulatory effects (A scale), euphoria (MBG scale), and somatic symptoms (LSD scale).

TABLE 1

Results of the statistical analyses performed on raw HRS scores, transformed ARCI scores (differences from predrug values), VAS measures (peak values and AUC_{0-8h}), and cardiovascular parameters (peak values and AUC_{0-4h})

For all measures $n = 18$.

Variable		ANOVA (2,34)		Tukey's Multiple Comparison Test		
				Placebo		Low Dose/High
		F	p Value	Low Dose	High Dose	
HRS						
Affect		29.35	<0.001	**	**	**
Cognition		31.66	<0.001	*	**	**
Somaesthesia		39.62	<0.001	**	**	**
Perception		38.76	<0.001	**	**	**
Volition		4.68	0.016	N.S.	*	N.S.
Intensity		77.35	<0.001	**	**	**
ARCI						
A		23.10	<0.001	*	**	**
BG		3.62	0.058			
LSD		10.05	<0.001	*	**	N.S.
MBG		11.22	<0.001	N.S.	**	N.S.
PCAG		0.91	0.412			
VAS						
Any Effect	Peak	39.62	<0.001	**	**	**
	AUC	18.06	<0.001	*	**	**
Good Effects	Peak	26.64	<0.001	**	**	*
	AUC	18.69	<0.001	**	**	*
Liking	Peak	29.82	<0.001	**	**	*
	AUC	15.10	<0.001	**	**	N.S.
Visions	Peak	16.28	<0.001	**	**	*
	AUC	7.25	0.002	N.S.	**	N.S.
Drunken	Peak	6.26	0.005	N.S.	**	N.S.
	AUC	4.83	0.014	N.S.	*	N.S.
Stimulated	Peak	16.62	<0.001	**	**	*
	AUC	11.57	<0.001	N.S.	**	*
High	Peak	33.97	<0.001	**	**	**
	AUC	22.33	<0.001	*	**	**
Cardiovascular						
SBP	Peak	2.91	0.068			
	AUC	1.90	0.166			
DBP	Peak	15.54	<0.001	**	**	N.S.
	AUC	5.59	0.008	*	*	N.S.
HR	Peak	1.79	0.183			
	AUC	3.12	0.057			

* $p < 0.05$; ** $p < 0.01$.

TABLE 2

Positive responses on particular items of the HRS questionnaire given by at least 75% of the 18 volunteers after the high ayahuasca dose

Each column indicates the number of subjects who reported the effect, regardless of intensity, at the two different ayahuasca doses administered and placebo. The letter in parentheses indicates the HRS scale in which the item belongs.

	Item	Placebo	0.6 mg/kg	0.85 mg/kg
1	High (I)	1/18	15/18	17/18
2	Body feels different (S)	4/18	12/18	17/18
3	Visual effects (P)	2/18	10/18	17/18
4	A “rush” (S)	0/18	9/18	17/18
5	Change in rate of time passing (C)	2/18	12/18	16/18
6	Eyes open visual field vibrating or jiggling (P)	2/18	10/18	15/18
7	Electric/tingling feeling (S)	1/18	9/18	15/18
8	Change in quality of thinking (C)	2/18	8/18	15/18
9	Change in visual distinctiveness of objects in room (P)	4/18	7/18	15/18
10	Sounds in room sound different (P)	2/18	5/18	15/18
11	Urge to close eyes (V)	5/18	8/18	14/18
12	Change in distinctiveness of sounds (P)	2/18	7/18	14/18
13	Change in rate of thinking (C)	1/18	7/18	14/18
14	Excited (A)	1/18	7/18	14/18

A, Affect; C, Cognition; I, Intensity; P, Perception; S, Somaesthesia; V, Volition.

Scores on the BG and PCAG scales were not significantly different from placebo.

Scorings on all seven VAS items showed significant drug effects (peak values and AUC) and significant drug by time interactions. Initial effects appeared between 30 and 45 min, reflected as rises in the VAS any effect item, and were followed by a prominent increase at around 60 min, as indicated by steep rises in all seven VAS items. In general terms, the maximum scorings were observed between 90 and 120 min after drug administration. A gradual return to baseline levels followed thereafter and was complete at 360 min. Regarding effect magnitude, the largest scores were obtained for the VAS any effect, liking, and high, followed by VAS good effects, visions, and stimulated items. The least modified VAS after ayahuasca administration was the drunken item.

More qualitative information on the nature of the effects brought about by ayahuasca is provided in Table 2, which lists the most frequently reported positive responses to specific items of the HRS questionnaire.

Cardiovascular Effects. Mean values for systolic (SBP) and diastolic blood pressure (DBP) and heart rate (HR) over time are presented in Fig. 3, and results of the statistical analysis performed are shown in Table 1.

Ayahuasca administration produced only moderate elevations of cardiovascular parameters. Statistically significant changes relative to placebo were only found for DBP, both for peak values and AUC. The largest difference in DBP between the low dose and placebo was 9 mm Hg and occurred at 75 min after dosing. Between the high dose and placebo, differences of 10 and 9 mm Hg were observed at 15 and 75 min, respectively. A maximal increase of 7 mm Hg from baseline values was observed at 60 min for the low dose. After the high dose, a maximal increase of 9 mm Hg was observed at 15 min. For SBP, the largest differences with placebo were observed at 75 min and corresponded to 4 and 6 mm Hg increases for the low and high dose, respectively. Similarly, the maximal increase in SBP relative to baseline values was observed at 75 min and corresponded to 6 and 8 mm Hg for the low and high dose, respectively. Finally, HR showed the largest differences with placebo at 60 min and corresponded to 5 and 4 beats/min increases for the low and the high ayahuasca doses, respectively. The maximal increase from baseline values observed for HR was 4 beats/min and occurred at 60 min after administration of both the low and high ayahuasca doses.

Only two volunteers showed SBP values equal to or above 140 mm Hg at any time point: volunteer 1 at 75 and 90 min (140 mm Hg) after receiving the low dose, and at 60 (146 mm Hg) and 75 min (140 mm Hg) after receiving the high dose; and volunteer 6 as early as 15 min after administration of the high ayahuasca dose (146 mm Hg). Two volunteers showed DBP above 90 mm Hg: volunteer 1 at 30 min (93 mm Hg) after the low dose, and at 15 min (96 mm Hg) after the high dose; and volunteer 15 at 120 and 150 min (95 and 92 mm Hg, respectively) after administration of the high dose. Regarding HR, volunteer 1 also showed values above 100 beats/min (101 beats/min) at 60 min after the high dose.

Urine Monoamine Metabolites. Urine samples were successfully collected for 15 of the 18 volunteers enrolled in the study, and results are given for this subgroup only. Statistical analyses showed a significant effect of drug only for normetanephrine. No significant drug by time interaction was found for any of the metabolites studied. In view of this, the total monoamine metabolite amounts excreted during the 0- to 24-h period after placebo and the two ayahuasca doses are presented in Table 3. As shown therein, rather than the expected decreases in deaminated metabolites (VMA, HVA, 5-HIAA), drug administration increased the excretion of these compounds nonsignificantly. Similarly, levels of the *O*-methylated metabolites metanephrine and normetanephrine increased with dose, although only the latter showed statistically significant differences with placebo.

Pharmacokinetics. The time course of plasma concentrations and the calculated pharmacokinetic parameters for DMT, harmaline, THH, harmol, and harmalol are shown in Fig. 4 and Table 4. The graphs correspond to 15 of the total 18 participants enrolled in the study. To avoid the miscalculation of pharmacokinetic parameters, data from three volunteers were excluded from the analysis due to vomiting occurring after administration of the low dose (volunteer 6) and the high dose (volunteers 4 and 18). An additional subject (volunteer 12) was excluded from the calculation of harmalol parameters. Plasma levels for this volunteer after the high dose showed a plateau between 6 and 24 h, precluding parameter assessment.

As shown in Table 4, C_{max} and AUC values increased with

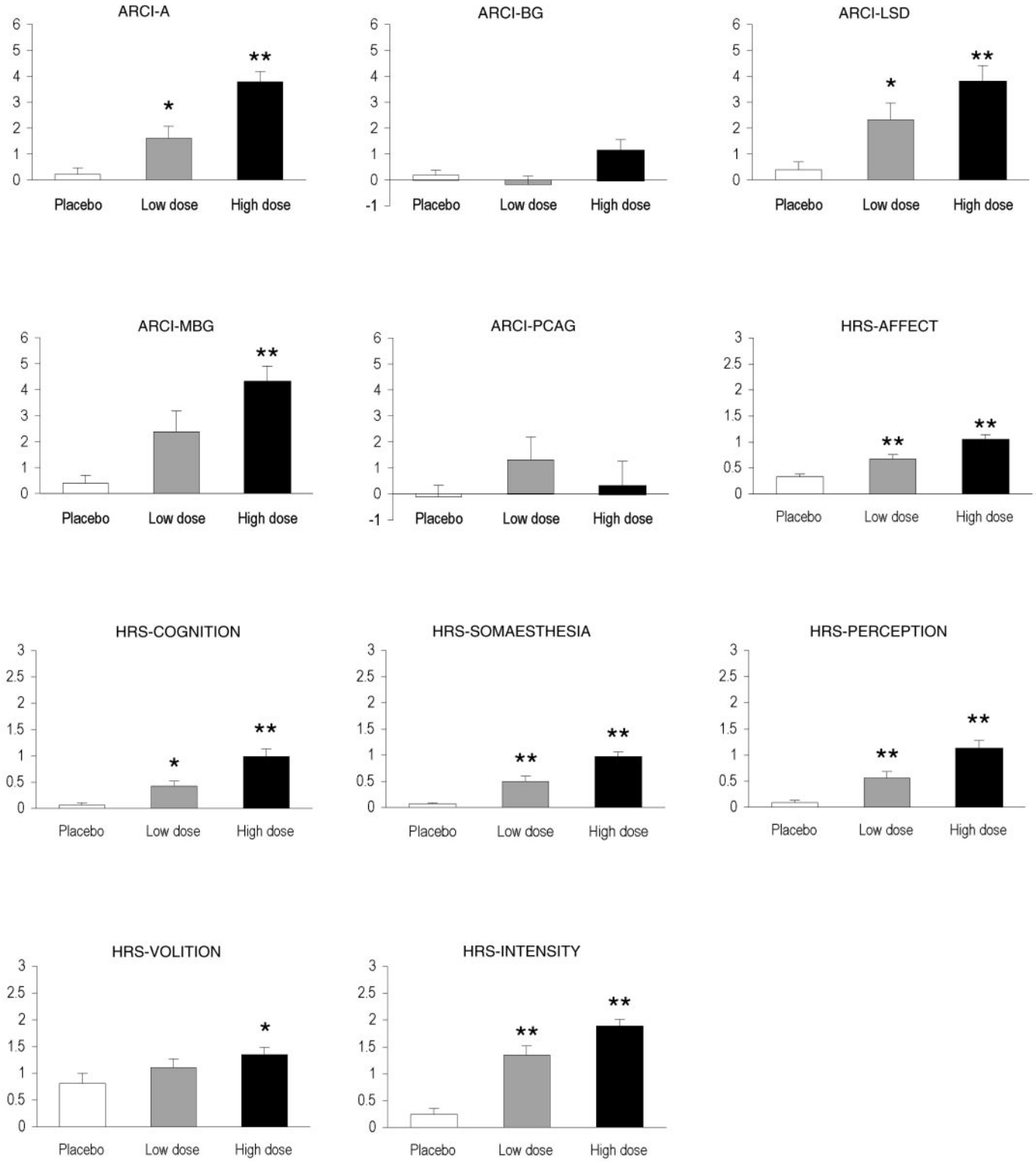

Fig. 1. Mean scores on the ARCI and HRS scales after administration of placebo (white), 0.6 mg of DMT/kg of body weight ayahuasca (shaded), and 0.85 mg of DMT/kg of body weight ayahuasca (black). Error bars denote 1 S.E.M. ($n = 18$). Significant differences from placebo are indicated by one ($p < 0.05$) or two ($p < 0.01$) asterisks.

dose for all measured compounds. DMT showed a T_{max} of 1.5 h (median) after both the low and high doses. Nevertheless, the upper end of the range of T_{max} values increased with dose, and the Wilcoxon test indicated a statistically significant difference between doses. A larger T_{max} after the high ayahuasca dose is evident also in the DMT concentration-time curve included in Fig. 4. Both harmaline and THH plasma concentrations peaked later than DMT, and their T_{max} values were larger after the high relative to the low ayahuasca dose. An unexpected finding was the absence of

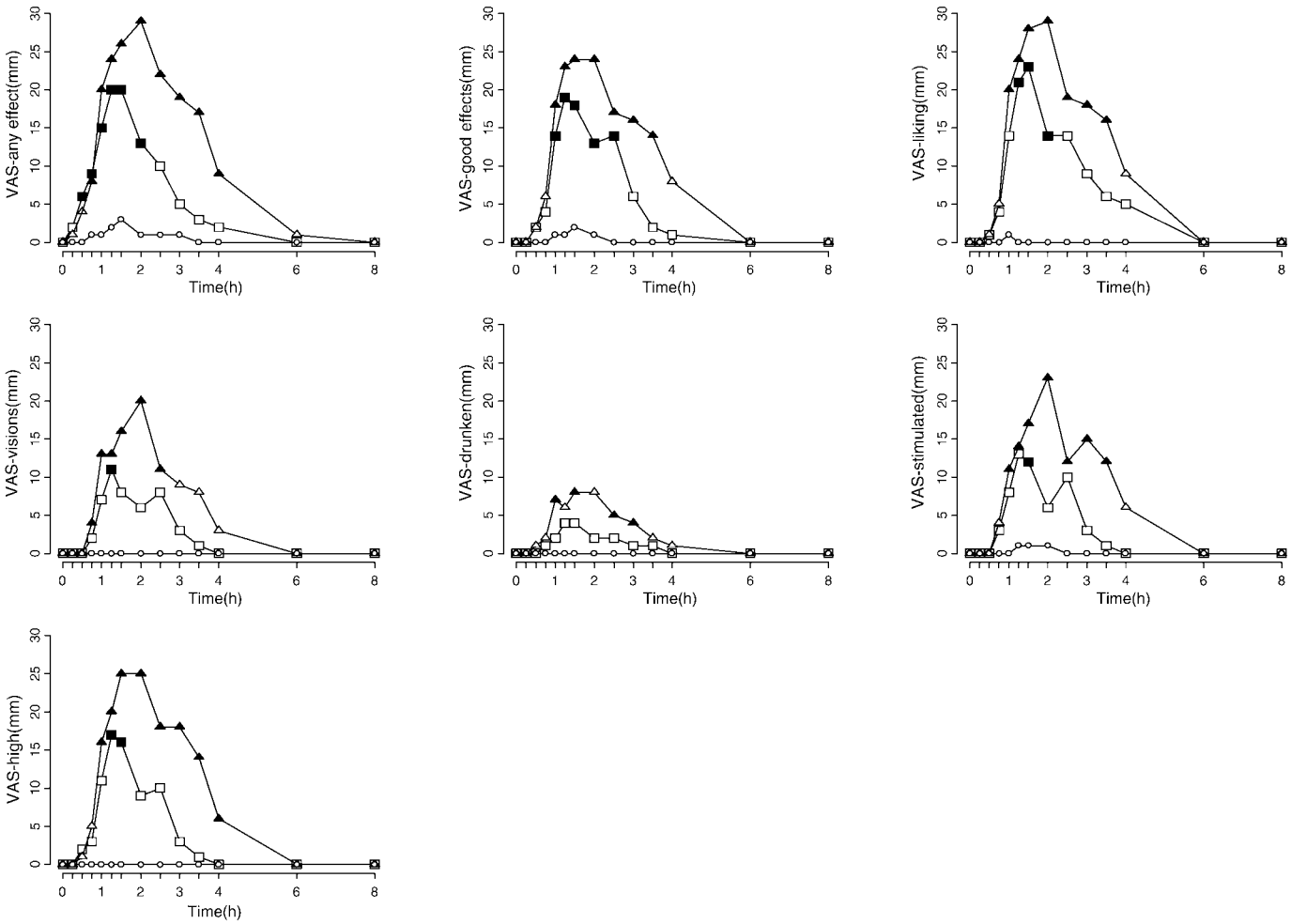

Fig. 2. Time curves of scores on the seven VAS items (means from 18 volunteers) after administration of placebo (circle), 0.6 mg of DMT/kg of body weight ayahuasca (square), and 0.85 mg of DMT/kg of body weight ayahuasca (triangle). Filled symbols indicate a significant difference from placebo.

measurable harmine plasma levels except for a few time points in 4 of 18 volunteers, precluding the calculation of pharmacokinetic parameters for this alkaloid.

Interestingly, all volunteers showed measurable levels of harmol, the *O*-demethylated analog of harmine. Plasma concentrations showed dose-dependent increases and peaked at 1.5 and 2 h after the low and high doses, respectively. Harmalol, the *O*-demethylated analog of harmaline, could also be quantified. Maximum concentrations were attained later than for harmaline, with T_{max} observed at 2.5 and 2.75 h after the low and high dose, respectively.

The AUC normalized by dose was calculated for each parent alkaloid, and these values were compared between doses by means of a paired Student's *t* test. A statistically significant difference was found for DMT, suggesting a possible nonproportional increase of plasma levels between doses. In line with this possibility, mean V_z/F and CL/F values calculated for DMT decreased with dose. These decreases were statistically significant for V_z/F and showed a tendency for CL/F ($t(14) = 1.94$, $p = 0.073$).

In support of a parallel evolution of DMT plasma levels and subjective effects, no significant differences were found between DMT T_{max} values and any of the seven VAS t_{max} values at any of the two administered ayahuasca doses.

Discussion

The psychotropic effects of ayahuasca could be demonstrated in a group of experienced psychedelic users who, in their vast majority, had reported no prior exposure to the tea. Oral administration of the freeze-dried material induced feelings of increased activation (ARCI-A, VAS-stimulated), euphoria and well being (ARCI-MBG, VAS-high, VAS-liking, VAS-good effects), and somatic effects (ARCI-LSD), in addition to perceptual modifications (HRS-Perception, VAS-visions) and changes in thought content (HRS-Cognition) and increased emotional lability (HRS-Affect). Increases in VAS-high have been observed after a great variety of drugs including MDMA (Camí et al., 2000), cocaine (Farré et al., 1993), and the sedative flunitrazepam (Farré et al., 1998). The VAS-stimulated item reflects more specifically the effects of psychostimulants such as amphetamine and MDMA (Camí et al., 2000). Increases in VAS-drunken, which was the least modified VAS item by ayahuasca, have been observed mainly after sedatives, such as flunitrazepam (Farré et al., 1998), and alcohol (Farré et al., 1993), but also after 125 mg of MDMA (Camí et al., 2000). Regarding the HRS, our findings are in line with results by other researchers who have demonstrated statistically significant increases in all HRS

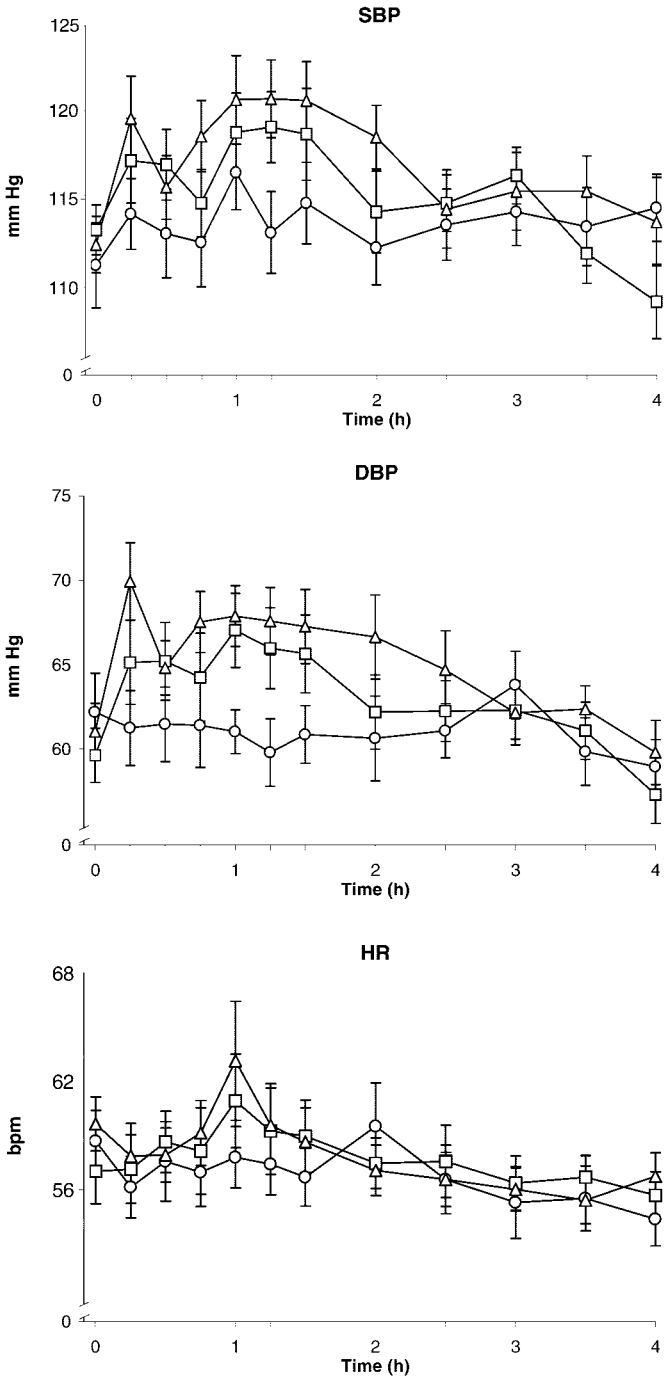

Fig. 3. Time course of cardiovascular measures (means from 18 volunteers) after administration of placebo (circle), 0.6 mg of DMT/kg of body weight ayahuasca (square), and 0.85 mg of DMT/kg of body weight ayahuasca (triangle). Error bars denote ± 1 S.E.M. (n = 18).

scales after the administration of various psychedelics, such as i.v. DMT and oral psilocybin (Strassman et al., 1994; Gouzoulis-Mayfrank et al., 1999). However, ayahuasca differed from these drugs in the time course of effects. The overall duration was longer than that of i.v. DMT, but shorter than that of mescaline or LSD (Strassman, 1994). Finally, regarding the ARCI questionnaire, increases in the ARCI-A, ARCI-BG, and ARCI-MBG scales are a common feature of psychostimulants (Martin et al., 1971; Lamas et al., 1994). However, in contrast, with drugs like amphetamine, methamphetamine, ephedrine, and methylphenidate (Martin et al., 1971), ayahuasca did not induce significant increases in the ARCI-BG scale, a measure of subjectively perceived improvement in intellectual efficiency. The coexistence of drug-induced stimulation with a wide range of modifications in the sensorium places ayahuasca among the psychedelics, a drug class which shares arousing properties with psychostimulants (Brawley and Duffield, 1972).

The present results on the subjective effects induced by ayahuasca in a clinical research setting replicate those obtained in a preliminary study involving a smaller sample of volunteers with prior experience with ayahuasca, and with a single-blind nonrandomized design (Riba et al., 2001b). In the previous study, statistically significant increases were observed in all HRS items, except volition, and in the ARCI-MBG, ARCI-LSD, and ARCI-A scales. In the present study, however, scores on these measures at the 0.6 and 0.85 mg of DMT/kg doses tended to be lower than those obtained after 0.5 and 0.75 mg of DMT/kg doses, respectively. Several factors such as sample size, study design, and prior exposure to ayahuasca could account for these differences. Scores on the HRS items at the present low dose were also lower than those reported by Grob et al. (1996), except for the somaesthesia and perception items, after the administration of an equivalent ayahuasca dose, in terms of DMT content, to a group of experienced long-term ritual users. Nevertheless, scores on all HRS items after the present high dose were higher than those reported by these researchers. Compared with i.v. DMT as described by Strassman et al. (1994), ayahuasca evokes effects of milder intensity, which show a slower onset and a longer overall duration. Scorings on the six HRS scales after the present high dose fell between those reported after 0.1 and 0.2 mg/kg i.v. DMT.

In our previous study on ayahuasca (Riba et al., 2001b), we failed to observe statistically significant modifications of cardiovascular parameters in a five-subject sample. In the present work, only modifications in DBP reached statistical significance. Increases in DBP, SBP, and HR were milder than those reported for other more prototypical sympathomimetics, such as amphetamine or MDMA, at doses showing psychotropic properties (Mas et al., 1999; de la Torre et al., 2000). DBP increases from baseline values after both ayahuasca doses were somewhat lower than the elevations from baseline values reported by Callaway et al. (1999) after an ayahuasca dose containing 0.48 mg of DMT/kg but larger amounts of β-carbolines.

The time course of DMT plasma concentrations closely paralleled that of subjective effects. The steep rise in DMT plasma levels observed at 1 h coincided with an analogous rise in VAS scores, and peak DMT concentrations and peak effects were obtained between 1.5 and 2 h. In the present study, quantifiable plasma levels were observed for DMT and THH. T_{max} values for DMT and THH were similar to those reported by Callaway et al. (1999). However, C_{max} values for DMT and THH in the present study were lower than expected, even after taking into account the smaller amounts administered in the case of THH. This could be due to a lower alkaloid bioavailability from the lyophilizate compared with the aqueous solution administered by Callaway et al. (1999). The calculated V_z/F values are similar in both studies, but Callaway et al. (1999) reported higher $t_{1/2}$ and lower CL/F values. In the case of DMT, these differences may be associ-

TABLE 3

Urinary excretion of monoamine metabolites pooled from 0 to 24 h after placebo, 0.6 mg, and 0.85 mg of DMT/kg of body weight ayahuasca

Figures indicate mean values (95% confidence interval), expressed in micromoles, from 15 volunteers.

Metabolite	ANOVA		Placebo	Tukey's Multiple Comparison test		
				Placebo		Low Dose/High
	F	*p* Value		Low Dose	High Dose	
VMA	0.61	0.552	20.21 (15.58–32.91)	22.54 (15.11–33.41)	23.31 (14.76–33.30)	
HVA	0.17	0.843	30.32 (23.22–49.14)	32.73 (20.83–46.90)	34.36 (19.44–45.72)	
5-HIAA	1.21	0.313	35.73 (27.11–57.53)	37.30 (28.64–60.55)	43.07 (34.25–71.63)	
MN	1.94	0.163	0.52 (0.41–0.87)	0.56 (0.46–0.96)	0.62 (0.51–1.06)	
NMN	12.56	<0.001	1.06 (0.86–1.79)	1.18 (1.03–2.09)	1.40** (1.22–2.48)	*

MN, metanephrine; NMN, normetanephrine.

* $p < 0.05$; ** $p < 0.01$.

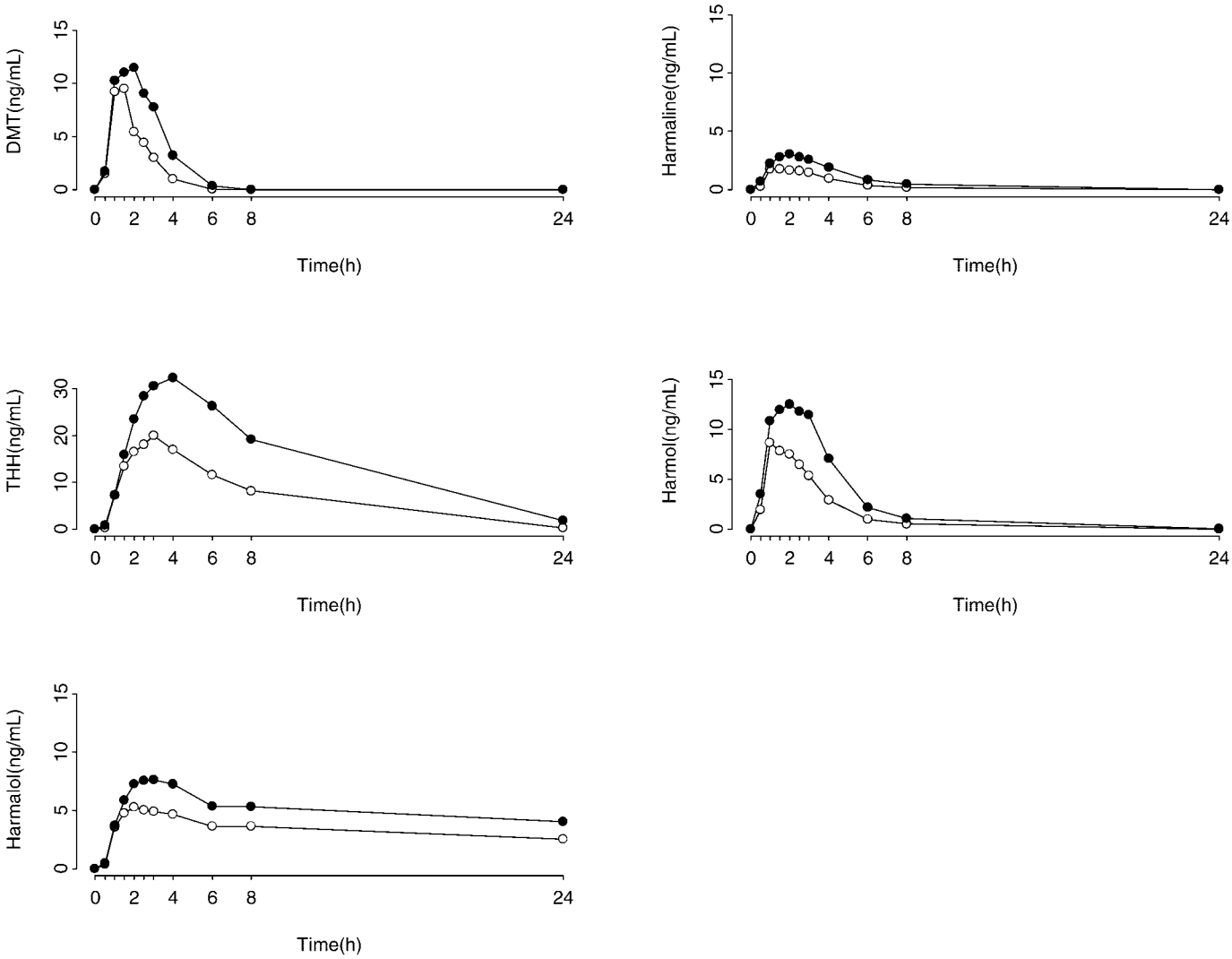

Fig. 4. Plasma concentration-time curves ($n = 15$) for three of the four main alkaloids present in ayahuasca (DMT, harmaline, and THH) and the *O*-demethylated analogs of harmine (harmol) and harmaline (harmalol). Open circles, low 0.6 mg of DMT/kg dose of ayahuasca; filled circles, high 0.85 mg DMT/kg dose of ayahuasca.

ated with the lower levels of harmala alkaloids present in our ayahuasca and the consequent lower degree of MAO inhibition. In addition to these interstudy differences, it is interesting to note that the normalized AUC calculated for DMT in the present study showed a statistically significant increase between the low and the high ayahuasca doses. This is suggestive of a nonlinear increment of DMT levels following the administration of increasing doses of ayahuasca. Considering that both V_z/F and CL/F decreased in a similar proportion between doses, these data could be interpreted as indicating a greater DMT bioavailability following the high dose, probably related to the higher amounts of harmala alkaloids ingested, leading to more effective MAO inhibition.

Another relevant difference from the study by Callaway et al. (1999) is the lack of measurable concentrations of harmine in plasma and the presence of significant levels of harmol and

TABLE 4

Pharmacokinetic parameters for DMT, harmaline, THH, harmol, and harmalol calculated for each of the two administered ayahuasca doses

Values indicate mean (S.D.), except for T_{max}, where median (range) is given. Fifteen volunteers were included in the analysis except for harmalol, where parameters were calculated from 14 volunteers.

	C_{max}	T_{max}	AUC_{0-8h}	$AUC_{0-\infty}$	$AUC_{0-\infty}/D$	$t_{1/2\lambda z}$	CL/F	V_z/F
	ng/ml	*h*	*ng/ml · h*$^{-1}$	*ng/ml · h*$^{-1}$		*h*	*l/h*	*liters*
Low Dose								
DMT	12.14* (9.09)	1.5* (1–2.5)	18.84* (10.67)	21.55* (9.93)	0.0005* (0.0003)	1.07 (0.58)	2281.41 (1054.7)	3509.86* (2158.08)
Harmaline	2.48* (1.28)	1.5 (1–3)	7.02* (4.02)	8.13* (4.39)	0.0017 (0.0009)	2.01 (0.56)	745.76 (379.68)	2040.75* (1044.47)
THH	23.06* (11.45)	2.5* (1.5–3)	100.83* (58.20)	172.07* (123.75)	0.0030 (0.0021)	4.78 (3.45)	559.84 (408.74)	3069.87 (2551.81)
Harmol	10.95* (6.04)	1.5 (1–2.5)	27.08* (12.51)	28.33* (12.78)		1.64 (0.29)		
Harmalol	6.74* (3.52)	2.5* (1–4)	31.14* (15.91)	206.93 (165.97)		30.33 (20.53)		
High Dose								
DMT	17.44 (10.49)	1.5 (1–4)	33.17 (14.68)	38.33 (17.53)	0.0007 (0.0003)	1.06 (0.77)	1812.65 (803.66)	2505.97 (1529.11)
Harmaline	4.32 (2.43)	2 (1–4)	12.80 (5.75)	14.87 (7.34)	0.0023 (0.0012)	1.95 (0.81)	596.78 (370.42)	1439.23 (567.18)
THH	39.40 (20.63)	3 (1.5–6)	180.89 (106.51)	351.89 (255.44)	0.0046 (0.0034)	4.68 (1.52)	364.94 (291.34)	2072.70 (1044.60)
Harmol	17.57 (7.72)	2 (1–3)	49.97 (16.88)	52.27 (17.30)		1.49 (0.28)		
Harmalol	9.59 (4.17)	2.75 (1.5–4)	46.79 (20.60)	333.54 (304.94)		48.64 (77.09)		

* $p < 0.05$.

harmalol. Differences in ayahuasca harmine content alone cannot entirely explain the absence of this alkaloid in plasma, considering that THH was present in the lyophilizate in amounts similar to those of harmine and was later measurable in plasma. Thus, harmine was either not absorbed in the gastrointestinal tract or was extensively degraded by first-pass metabolism before reaching systemic circulation. The presence of harmol in plasma would support the second hypothesis. Harmol glucuronide and harmol sulfate have been described as the main urine metabolites of harmine following its i.v. administration in humans (Slotkin et al., 1970). A very recent study has found cytochrome P450 to catalyze the *O*-demethylation of harmine and harmaline, and has identified CYP2D6 and CYP1A1 as the major isoenzymes involved in the process (Yu et al., 2003). Nevertheless, we cannot conclude that harmine was completely metabolized to render harmol, because very small amounts of harmol and harmalol have been detected in *B. caapi* and ayahuasca (Rivier and Lindgren, 1972; McKenna et al., 1984). Thus, it cannot be entirely ruled out that at least part of the amounts found in plasma could have been ingested with the tea.

The low plasma levels found for harmine in the present study could explain the absence of a clear-cut MAO inhibitor effect on the urinary excretion of monoamine metabolites. The acute administration of a MAO-A inhibitor induces a decrease in the levels of oxidized deaminated monoamine metabolites and an increase in the levels of COMT-dependent methylated compounds (Pletscher, 1966; Koulu et al., 1989). Whereas in the present study normetanephrine, a methylated breakdown product of norepinephrine, showed statistically significant increases after dosing with ayahuasca, the levels of the deaminated metabolites measured, i.e., VMA, HVA, and 5-HIAA, did not show decreases but, rather, were nonsignificantly increased. It is thus unclear whether the observed neurotransmitter metabolite profile was secondary to MAO inhibition. An alternative explanation would be an increase in norepinephrine release induced by DMT, which would fit well the observed sympathomimetic properties of this compound. However, this assumption is not supported by the limited available evidence from related compounds. Results obtained in two studies involving LSD administration to humans found no drug effects on monoamine metabolite excretion (Hollister and Moore, 1967; Messiha and Grof, 1973), and to our knowledge, no data are available on the effects of parenteral DMT on these measures. In any case, MAO inhibition by ayahuasca alkaloids effectively facilitated the access of DMT to systemic circulation but may have been insufficiently potent or insufficiently prolonged to modify the profile of deaminated monoamine metabolites in the 8-h urine collection periods used.

To conclude, the present findings indicate that following ayahuasca administration to humans, measurable DMT plasma levels are obtained together with distinct psychedelic effects. Psychoactivity is attained with negligible levels of circulating harmine. These results and the lack of a clear-cut systemic MAO inhibitor effect are suggestive of a harmine-DMT interaction predominantly taking place in the gastrointestinal tract and possibly in the liver. Harmine effects at a peripheral level would appear to suffice to prevent first-pass metabolism of DMT and allow its access to the CNS in amounts able to evoke psychotropic effects.

Acknowledgments

We express gratitude to José María Fábregas, Félix González, and Esther Martínez for their support in the initial stages of the research project. We are also indebted to CEFLURIS in Brazil, who kindly provided the ayahuasca (Daime) used in the present study. We also acknowledge the support of James C. Callaway, Department of Pharmaceutical Chemistry, University of Kuopio, Finland, for quantifying the DMT in ayahuasca; María Montero, who conducted the psychiatric interviews with the volunteers; Josep Maria Queraltó, Biochemistry Department, Hospital de Sant Pau, Barcelona, for quantifying urine monoamine metabolites; and Sylvie Cotxet, David Martínez, and Llúcia Benito for collaboration in data collection, and Pablo Ayesta for editing the figures.

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