0022-3565/03/3061-73–83$7.00
THE JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS
Copyright © 2003 by The American Society for Pharmacology and Experimental Therapeutics
JPET 306:73–83, 2003

Vol. 306, No. 1
49882/1069698
Printed in U.S.A.

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

JORDI RIBA, MARTA VALLE, GLORIA URBANO, MERCEDES YRITIA, ADELAIDA MORTE, and MANEL J. BARBANOJ

Àrea d'Investigació Farmacològica, Institut de Recerca, Hospital de la Santa Creu i Sant Pau; and Departament de Farmacologia i Terapèutica, Universitat Autònoma de Barcelona, Barcelona, Spain

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

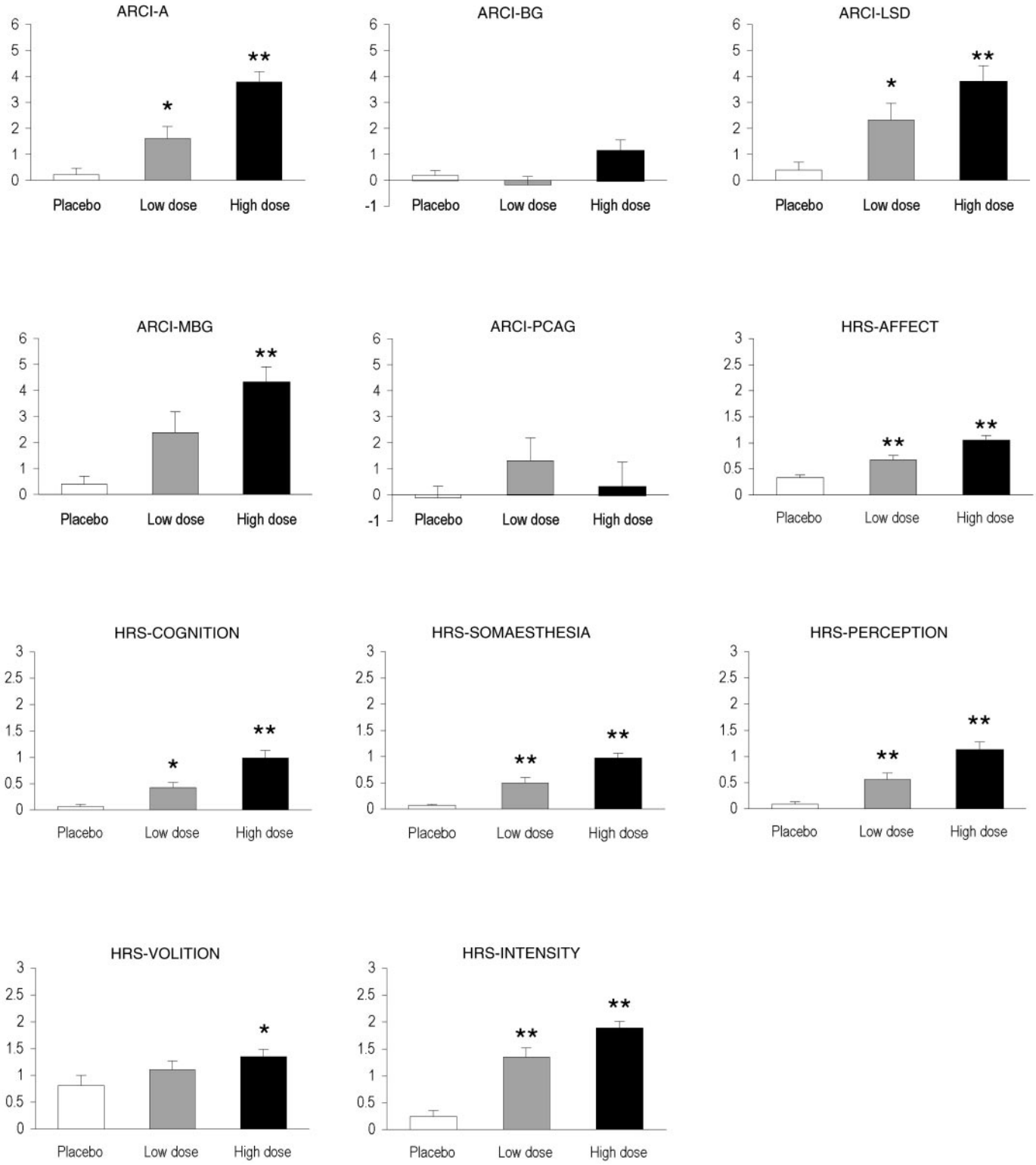

Fig. 1. Mean scores on the ARCI and HRS scales after administration of placebo (white), 0.6 mg of DMT/kg of body weight ayahuasca (shaded), and 0.85 mg of DMT/kg of body weight ayahuasca (black). Error bars denote 1 S.E.M. ($n = 18$). Significant differences from placebo are indicated by one ($p < 0.05$)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

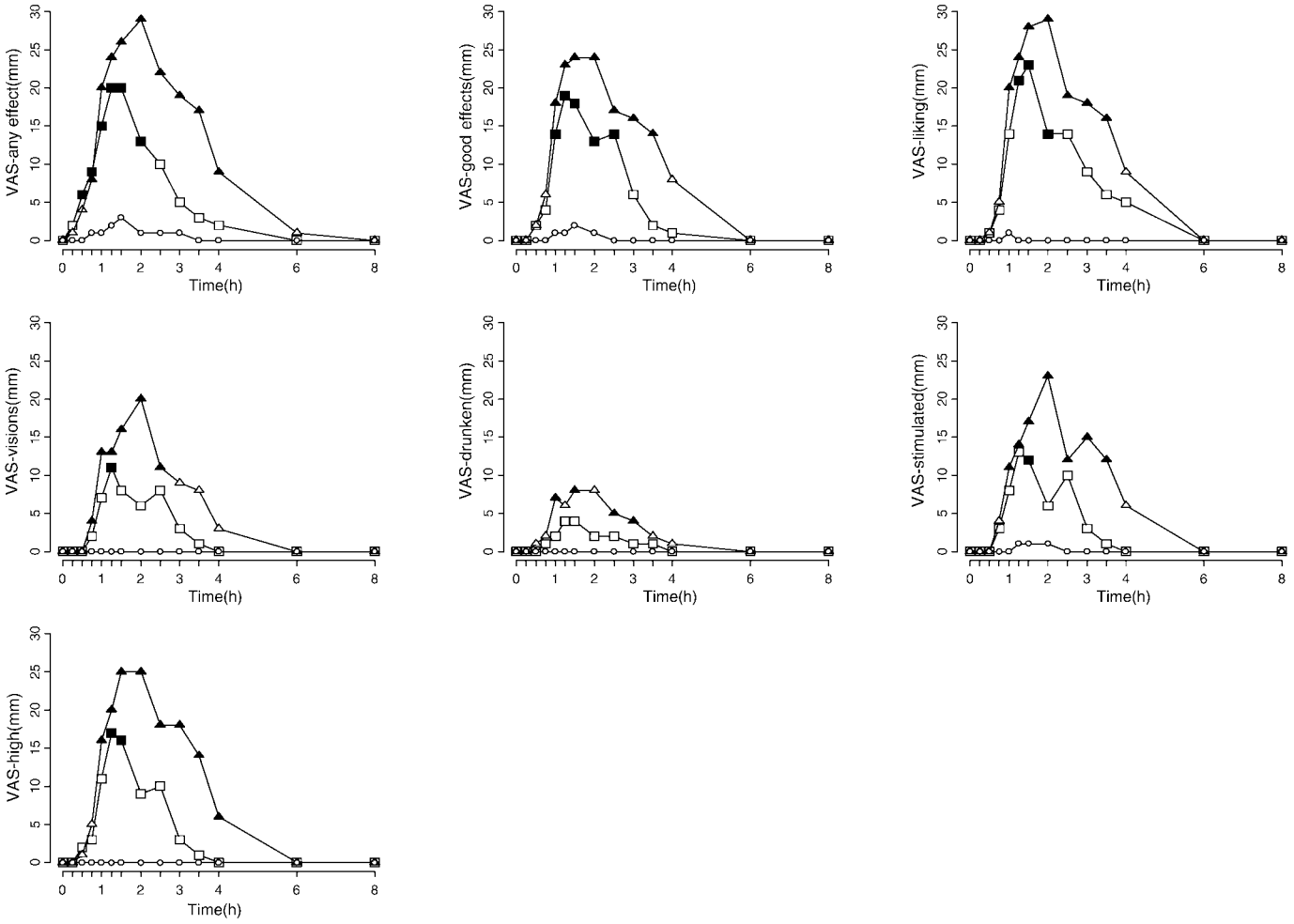

Fig. 2. Time curves of scores on the seven VAS items (means from 18 volunteers) after administration of placebo (circle), 0.6 mg of DMT/kg of body weight ayahuasca (square), and 0.85 mg of DMT/kg of body weight ayahuasca (triangle). Filled symbols indicate a significant difference from placebo.

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

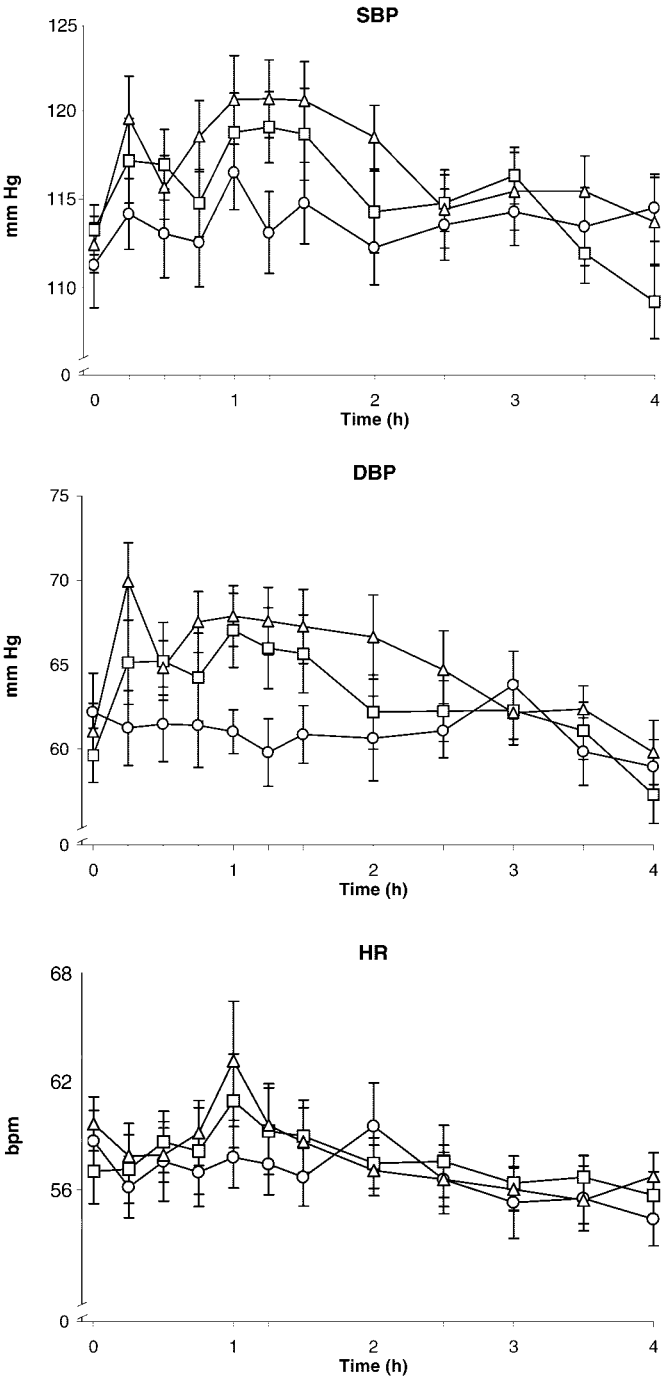

Fig. 3. Time course of cardiovascular measures (means from 18 volunteers) after administration of placebo (circle), 0.6 mg of DMT/kg of body weight ayahuasca (square), and 0.85 mg of DMT/kg of body weight ayahuasca (triangle). Error bars denote ± 1 S.E.M. (n = 18).

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

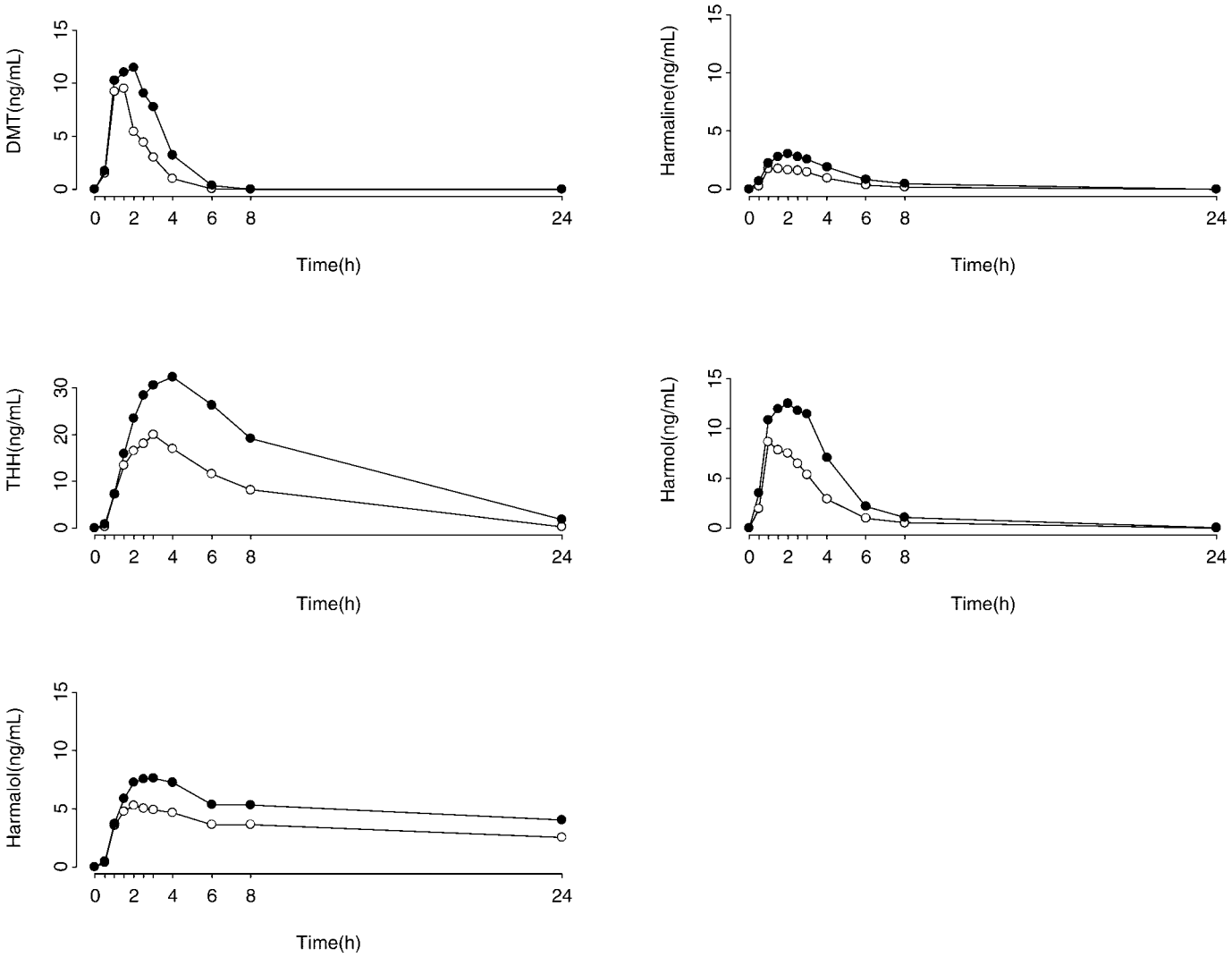

Fig. 4. Plasma concentration-time curves ($n = 15$) for three of the four main alkaloids present in ayahuasca (DMT, harmaline, and THH) and the *O*-demethylated analogs of harmine (harmol) and harmaline (harmalol). Open circles, low 0.6 mg of DMT/kg dose of ayahuasca; filled circles, high 0.85 mg DMT/kg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

References

Anonymous (2000) L'Ayahuasca: de l'Amazonie à la Jungle Urbaine, in *La Géopolitique Mondiale des Drogues 1998/1999*, pp 102–106, Observatoire Géopolitique des Drogues, Paris.

Brawley P and Duffield JC (1972) The pharmacology of hallucinogens. *Pharmacol Rev* **24:**31–66.

Buckholtz NS and Boggan WO (1977) Monoamine oxidase inhibition in brain and liver produced by β-carbolines: structure-activity relationships and substrate specificity. *Biochem Pharmacol* **26:**1991–1996.

Callaway JC, McKenna DJ, Grob CS, Brito GS, Raymon LP, Poland RE, Andrade EN, Andrade EO, and Mash DC (1999) Pharmacokinetics of *hoasca* alkaloids in healthy humans. *J Ethnopharmacol* **65:**243–256.

Callaway JC, Raymon LP, Hearn WL, McKenna DJ, Grob CS, Brito GC, and Mash DC (1996) Quantitation of *N,N*-dimethyltryptamine and harmala alkaloids in human plasma after oral dosing with *Ayahuasca*. *J Anal Toxicol* **20:**492–497.

Camí J, Farré M, Mas M, Roset PN, Poudevida S, Mas A, San L, and de la Torre R (2000) Human pharmacology of 3,4-methylenedioxymethamphetamine ("ecstasy"): psychomotor performance and subjective effects. *J Clin Psychopharmacol* **20:**455–466.

de la Torre R, Farré M, Roset PN, Hernández López C, Mas M, Ortuño J, Menoyo E,

Pizarro N, Segura J, and Camí J (2000) Pharmacology of MDMA in humans. *Ann NY Acad Sci* **914:**225–237.
Dobkin de Rios M (1984) *Visionary Vine: Hallucinogenic Healing in the Peruvian Amazon*. Waveland Press, Prospect Heights, IL.
Dobkin de Rios M (1996) Commentary on "Human pharmacology of Hoasca": a medical anthropology perspective. *J Nerv Ment Dis* **184:**95–98.
Farré M, de la Torre R, Llorente M, Lamas X, Ugena B, Segura J, and Camí J (1993) Alcohol and cocaine interactions in humans. *J Pharmacol Exp Ther* **266:**1364–1373.
Farré M, Terán MT, Roset PN, Mas M, Torrens M, and Camí J (1998) Abuse liability of flunitrazepam among methadone-maintained patients. *Psychopharmacology* **140:**486–495.
Gamache PH, Kingery ML, and Acworth IN (1993) Urinary metanephrine and normetanephrine determined without extraction by using liquid chromatography and coulometric array detection. *Clin Chem* **39:**1825–1830.
Gouzoulis-Mayfrank E, Thelen B, Habermeyer E, Kunert HJ, Kovar KA, Lindenblatt H, Hermle L, Spitzer M, and Sass H (1999) Psychopathological, neuroendocrine and autonomic effects of 3,4-methylenedioxyethylamphetamine (MDE), psilocybin and *d*-methamphetamine in healthy volunteers. *Psychopharmacology* **142:**41–50.
Grob CS, McKenna DJ, Callaway JC, Brito GS, Neves ES, Oberlaender G, Saide OL, Labigalini E, Tacla C, Miranda CT, et al. (1996) Human psychopharmacology of hoasca, a plant hallucinogen used in ritual context in Brazil. *J Nerv Ment Dis* **184:**86–94.
Hollister LE and Moore F (1967) Urinary catecholamine excretion following lysergic acid diethylamide in man. *Psychopharmacologia* **11:**270–275.
Koulu M, Scheinin M, Kaarttinen A, Kallio J, Pyykkö K, Vuorinen J, and Zimmer RH (1989) Inhibition of monoamine oxidase by moclobemide: effects on monoamine metabolism and secretion of anterior pituitary hormones and cortisol in healthy volunteers. *Br J Clin Pharmacol* **27:**243–255.
Lamas X, Farré M, Llorente M, and Camí J (1994) Spanish version of the 49-item short form of the Addiction Research Center Inventory. *Drug Alcohol Depend* **35:**203–209.
Martin WR, Sloan JW, Sapira JD, and Jasinski DR (1971) Physiologic, subjective, and behavioral effects of amphetamine, methamphetamine, ephedrine, phenmetrazine and methylphenidate in man. *Clin Pharmacol Ther* **12:**245–258.
Mas M, Farré M, de la Torre R, Roset PN, Ortuño J, Segura J, and Camí J (1999) Cardiovascular and neuroendocrine effects and pharmacokinetics of 3,4-methylenedioxymethamphetamine in humans. *J Pharmacol Exp Ther* **290:**136–145.
McKenna DJ, Towers GHN, and Abbott F (1984) Monoamine oxidase inhibitors in South American hallucinogenic plants: tryptamine and β-carboline constituents of *ayahuasca*. *J Ethnopharmacol* **10:**195–223.
Messiha FS and Grof S (1973) D-Lysergic acid diethylamide (LSD)—effect on biogenic amines excretion in man. *Biochem Pharmacol* **22:**2352–2354.
Ott J (1999) Pharmahuasca: human pharmacology of oral DMT plus harmine. *J Psychoact Drugs* **31:**171–177.
Parker NC, Levtzow CB, Wright PW, Woodard LL, and Chapman JF (1986) Uniform chromatographic conditions for quantifying urinary catecholamines, metanephrines, vanillylmandelic acid, 5-hydroxyindoleacetic acid, by liquid chromatography, with electrochemical detection. *Clin Chem* **32:**1473–1476.
Pierce PA and Peroutka SJ (1989) Hallucinogenic drug interactions with neurotransmitter receptor binding sites in human cortex. *Psychopharmacology* **97:**118–122.
Pletscher A (1966) Monoamine oxidase inhibitors. *Pharmacol Rev* **18:**121–129.
Riba J, Rodríguez-Fornells A, Strassman RJ, and Barbanoj MJ (2001a) Psychometric assessment of the Hallucinogen Rating Scale. *Drug Alcohol Depend* **62:**215–223.
Riba J, Rodríguez-Fornells A, Urbano G, Morte A, Antonijoan R, Montero M, Callaway JC, and Barbanoj MJ (2001b) Subjective effects and tolerability of the South American psychoactive beverage *ayahuasca* in healthy volunteers. *Psychopharmacology* **154:**85–95.
Rivier L and Lindgren JE (1972) "Ayahuasca", the South American hallucinogenic drink: an ethnobotanical and chemical investigation. *Econ Bot* **26:**101–129.
Schultes RE and Hofmann A (1980) *The Botany and Chemistry of Hallucinogens*. Charles C. Thomas, Springfield, IL.
Schultes RE and Hofmann A (1982) *Plantas de los dioses: orígenes del uso de los alucinógenos*. Fondo de Cultura Económica, México D. F.
Slotkin TA, DiStefano V, and Au WYW (1970) Blood levels and urinary excretion of harmine and its metabolites in man and rats. *J Pharmacol Exp Ther* **173:**26–30.
Smith RL, Canton H, Barrett RJ, and Sanders-Bush E (1998) Agonist properties of *N,N*-dimethyltryptamine at serotonin 5-HT_{2A} and 5-HT_{2C} receptors. *Pharmacol Biochem Behav* **61:**323–330.
Soldin SJ and Hill JG (1980) Simultaneous liquid-chromatographic analysis for 4-hydroxy-3-methoxymandelic acid and 4-hydroxy-3-methoxyphenylacetic acid in urine. *Clin Chem* **26:**291–294.
Spielberger CD, Gorsuch RL, and Lushene RE (1970) *Manual for the State-Trait Anxiety Inventory*. Consulting Psychologists Press, Palo Alto.
Strassman RJ (1994) Human psychopharmacology of LSD, dimethyltryptamine and related compounds, in *50 Years of LSD: Current Status and Perspectives of Hallucinogens* (Pletscher A and Ladewig D eds) pp 145–174, Parthenon, London.
Strassman RJ and Qualls CR (1994) Dose-response study of *N,N*-dimethyltryptamine in humans. I. Neuroendocrine, autonomic and cardiovascular effects. *Arch Gen Psychiatry* **51:**85–97.
Strassman RJ, Qualls CR, Uhlenhuth EH, and Kellner R (1994) Dose-response study of *N,N*-dimethyltryptamine in humans. II. Subjective effects and preliminary results of a new rating scale. *Arch Gen Psychiatry* **51:**98–108.
Suzuki O, Katsumata Y, and Oya M (1981) Characterization of eight biogenic indoleamines as substrates for type A and type B monoamine oxidase. *Biochem Pharmacol* 30:1353–1358.
Yritia M, Riba J, Ortuño J, Ramirez A, Castillo A, Alfaro Y, de la Torre R, and Barbanoj MJ (2002) Determination of *N,N*-dimethyltryptamine and β-carboline alkaloids in human plasma following oral administration of *Ayahuasca*. *J Chromatogr Biomed Appl* **779:**271–281.
Yu A, Idle JR, Krausz KW, Kupfer A, and Gonzalez FJ (2003) Contribution of individual cytochrome P450 isoenzymes to the *O*-demethylation of the psychotropic β-carboline alkaloids harmaline and harmine. *J Pharmacol Exp Ther* **305:**315–322.

Address correspondence to: Manel J. Barbanoj, Àrea d'Investigació Farmacològica, Institut de Recerca, Hospital de la Santa Creu i Sant Pau., St. Antoni Maria Claret, 167, Barcelona 08025, Spain. E-mail: mbarbanoj@hsp.santpau.es