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ORIGINAL INVESTIGATION

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

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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

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 predrug 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

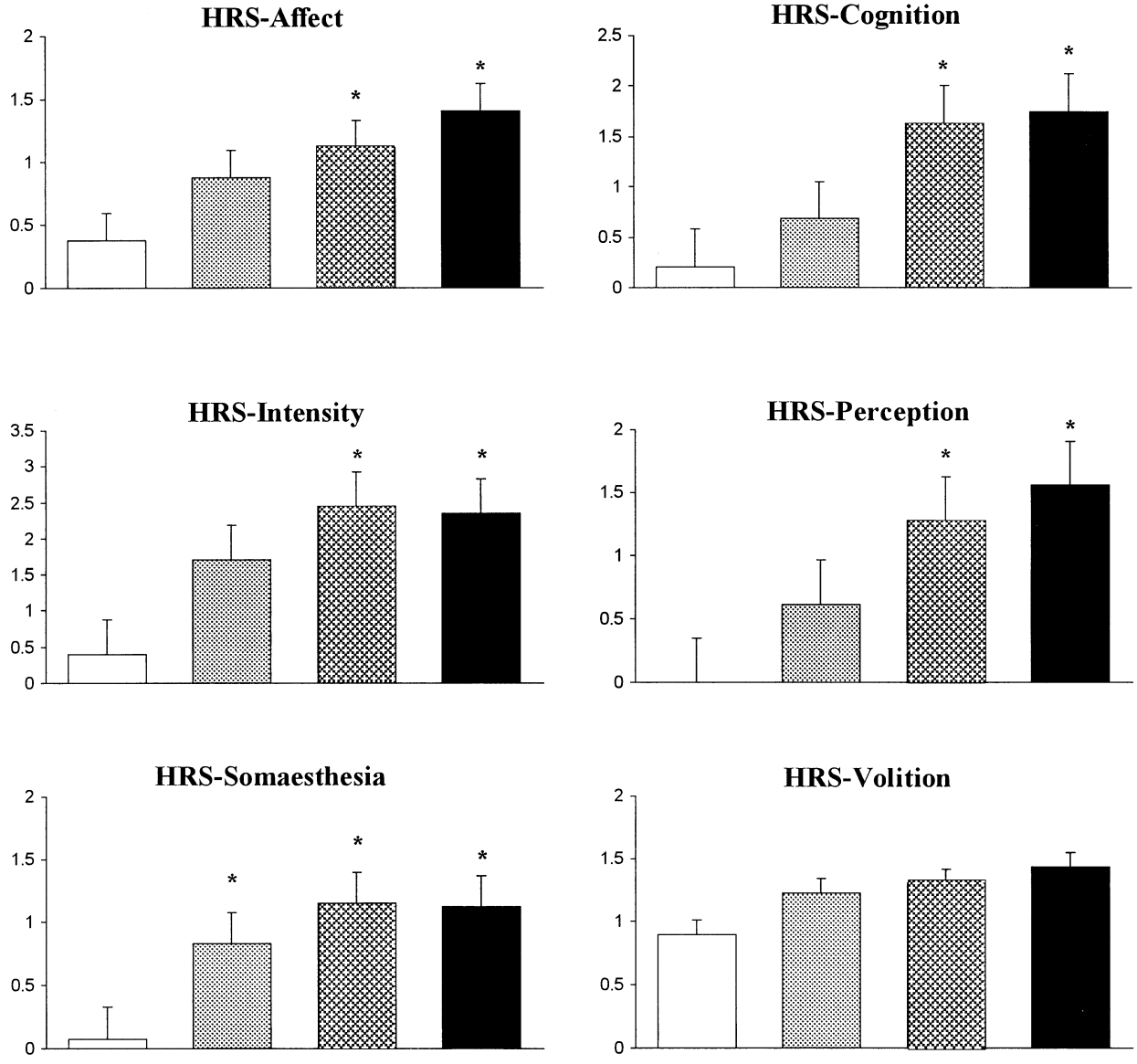

Fig. 1 Mean scores on the six Hallucinogen Rating Scale (HRS) subscales after administration of placebo (□), 0.5 mg *N,N*-dimethyltryptamine (DMT)/kg body weight *ayahuasca* (*lightly shaded*), 0.75 mg/kg (*shaded*), and 1.0 mg/kg (■). *Error bars* denote 1 standard error of mean (n=5). Significant differences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

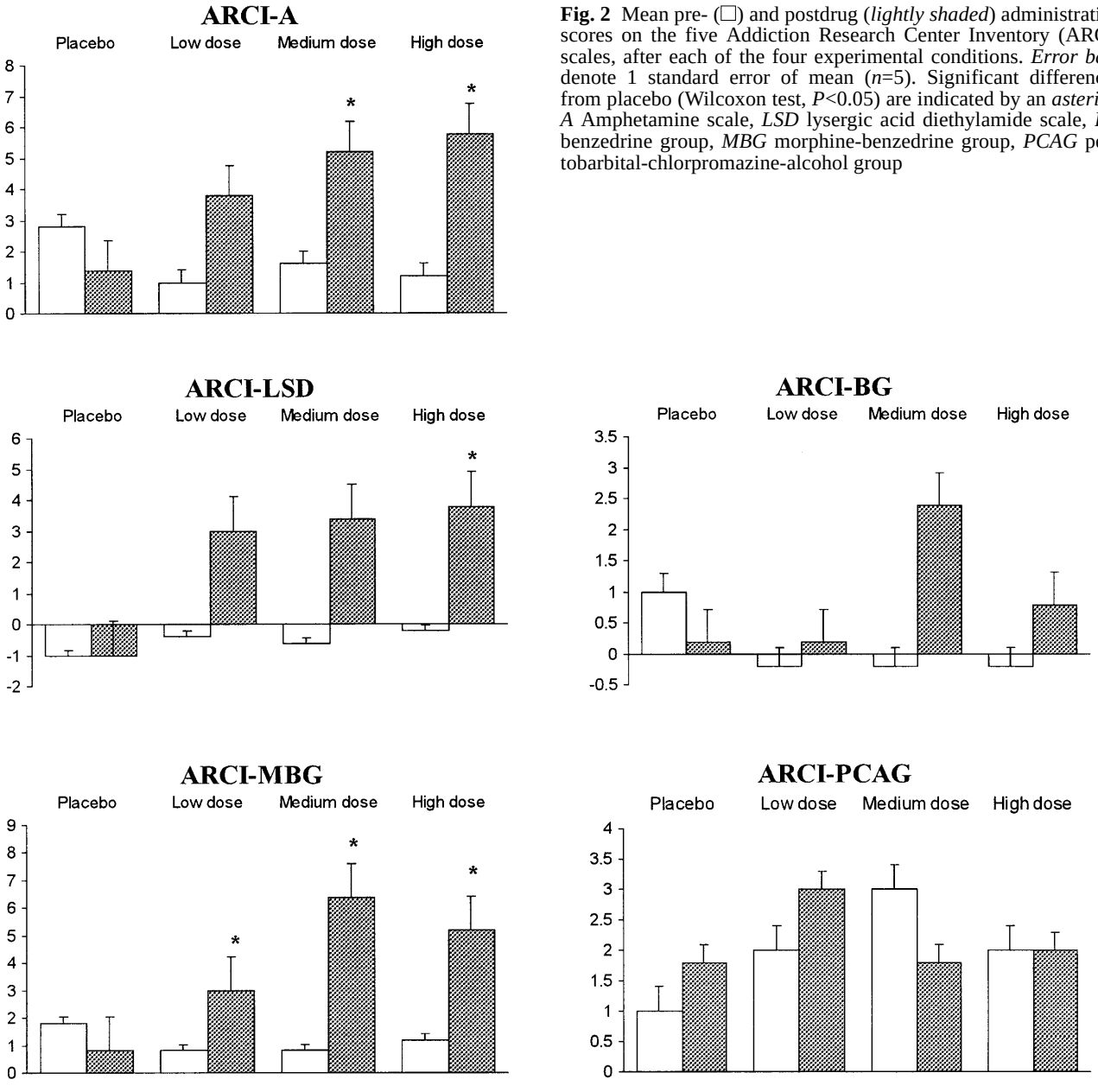

Fig. 2 Mean pre- (□) and postdrug (*lightly shaded*) administration scores on the five Addiction Research Center Inventory (ARCI) scales, after each of the four experimental conditions. *Error bars* denote 1 standard error of mean (n=5). Significant differences from placebo (Wilcoxon test, P<0.05) are 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-

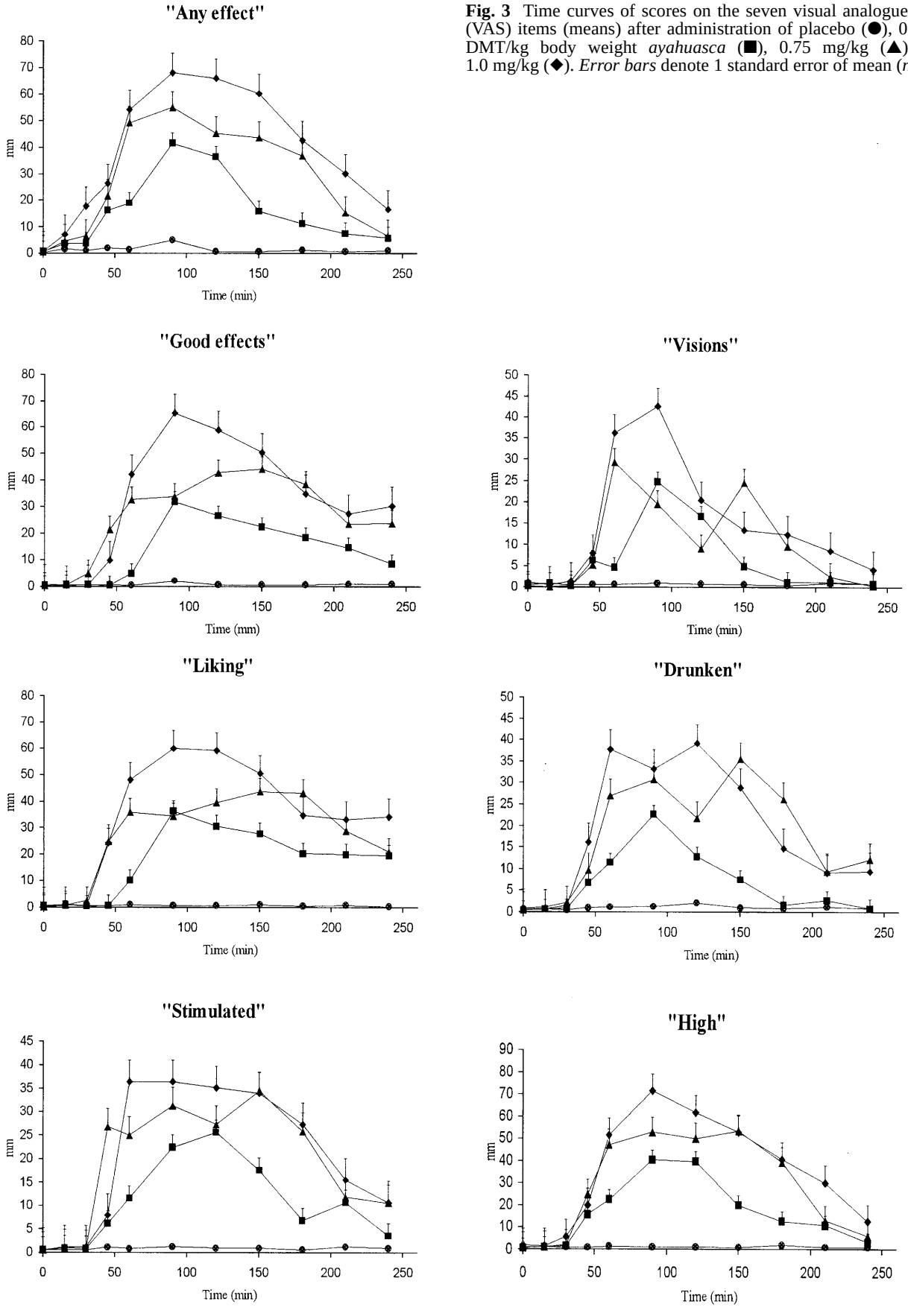

Fig. 3 Time curves of scores on the seven visual analogue scale (VAS) items (means) after administration of placebo (●), 0.5 mg DMT/kg body weight *ayahuasca* (■), 0.75 mg/kg (▲), and 1.0 mg/kg (◆). *Error bars* denote 1 standard error of mean (*n*=5)

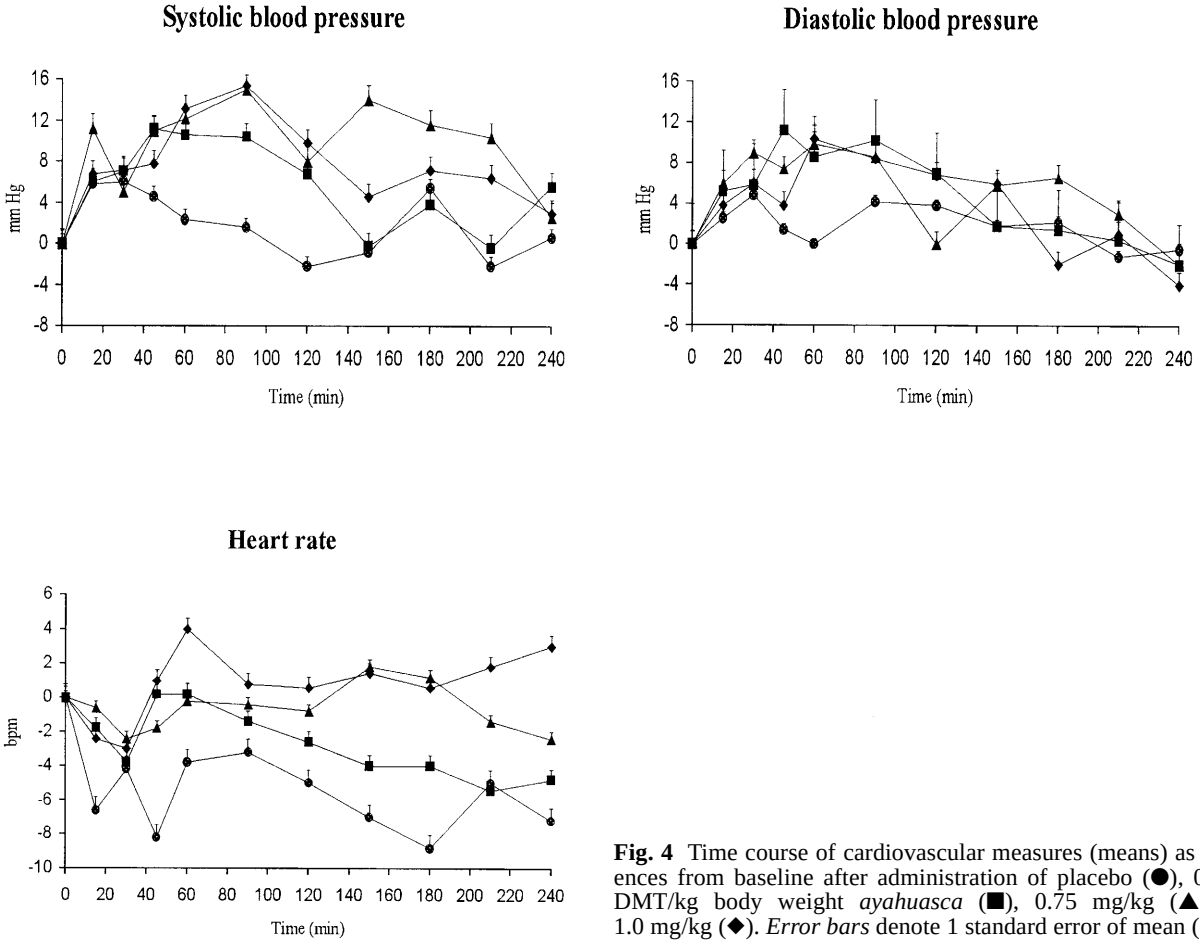

Fig. 4 Time course of cardiovascular measures (means) as differences from baseline after administration of placebo (●), 0.5 mg DMT/kg body weight *ayahuasca* (■), 0.75 mg/kg (▲), and 1.0 mg/kg (◆). *Error bars* denote 1 standard error of mean (n=5)

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.*

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