

DISCUSSION

The aim of the present study was to study the human pharmacology of *ayahuasca* in a controlled clinical trial. Working with the lyophilizate of the tea proved a convenient method for this purpose. However, the difficulties involved in the obtention, handling and storing of the freeze-dried material in order to administer accurate dosings in a standardized and stable pharmaceutical form, made this an achievement in itself. At the beginning of the research project, the option of studying combinations of pure DMT plus pure β -carbolines was considered. Although this approach would have simplified the matter enormously, it is our view that results from these preparations could not have been considered to fully reflect *ayahuasca* pharmacology. While some findings might not have changed much from one approach to the other, other aspects of the clinical picture certainly would have. A natural extract such as *ayahuasca* contains a myriad of substances. Some are pharmacologically active, but inert plant material is likely at least to influence the gastrointestinal tolerability of the tea. Although not ideal for the precise study of drug-drug interactions, ingestion of the natural tea may lead to a different experience in terms of unpleasant somatic effects, nausea or vomiting, compared with the simple combination of pure compounds in a capsule. The use of the lyophilizate thus appeared to be a reasonable compromise.

The constellation of subjective effects elicited by *ayahuasca* could be effectively quantified by means of the battery of self-administered instruments used for this purpose, i.e., the HRS, the ARCI and the VAS. The HRS was sensitive to *ayahuasca* effects, as it has previously been shown to be sensitive to other psychedelics such as i.v. DMT and oral psilocybin (Gouzoulis-Mayfrank et al., 1999b; Strassman et al., 1994). VAS data indicated that *ayahuasca* shows a distinct duration of effects, longer than those of i.v. DMT, but shorter than those of mescaline or LSD (Strassman, 1994). Finally, ARCI results revealed that *ayahuasca* effects are not merely perceptual, but share common features with psychostimulants (Martin et al., 1971) and elicit marked somatic-dysphoric symptoms. The coexistence of stimulation with modifications in the sensorium portrays *ayahuasca* as a psychedelic, and its subjective effects are dose-dependent and can be evidenced by the instruments used. This information being established for *ayahuasca*, blockade studies can be proposed in order to better characterize the neurochemical mechanisms involved in its effects. Additionally, we may now be able to address the long neglected study of the individual β -carbolines in humans and examine which of these and at what doses they can elicit subjective effects

analogous to those of *ayahuasca*, if at all. If the β -carbolines prove devoid of psychedelic activity, the use of subjective-effect measures combined with the administration of pure compounds may alternatively help tease apart the contribution of each of the β -carbolines in the facilitation of DMT absorption per os.

The EEG variables provided a quantitative and dose-dependent measure of *ayahuasca* effects on the CNS, which is totally objective and not easily influenced by the subject's expectations or will. Although complex, *ayahuasca* effects on the EEG power spectrum are compatible with its proposed neurochemical mechanism of action. Decreases in slow activity, i.e., delta and theta power, are a general feature of psychedelics displaying 5-HT₂ agonist activity, but also of psychostimulants such as amphetamine and methylphenidate, and serotonin releasers such as fenfluramine, (Herrmann and Schaerer, 1986; Itil and Fink, 1966; Saletu et al., 1993). Delta activity has traditionally been thought to reflect inhibitory activity, and increases in theta have been observed in relaxed and meditative states. Results thus suggest an excitatory or arousing effect for *ayahuasca*. This assumption is further supported by the fact that major tranquilizers with D₂ or mixed D₂/5-HT₂ antagonist activity, such as chlorpromazine and risperidone, are characterized by their delta and theta-promoting activity (Lee et al., 1999; Saletu et al., 1993). An important difference between *ayahuasca* and psychostimulants is the alpha-2 decreasing properties found in the present study. Early pharmacology-EEG research on LSD had also shown decreases in alpha activity after acute drug administration (Itil and Fink, 1966). Amphetamine, on the other hand, is known to enhance alpha in addition to its slow wave dampening effects, a feature not shared by *ayahuasca*. Future studies could benefit from comparing *ayahuasca* effects with those of more prototypical psychostimulants such as *d*-amphetamine. Besides, pretreatment with selective 5-HT_{2A} antagonists would allow for the identification of individual EEG variables specifically modified by 5-HT_{2A} activation.

The LORETA results obtained in the present study should be regarded as exploratory. The technique is relatively recent and this is the first time it has been applied to study *ayahuasca* or any other psychedelic. Based on the cortical areas targeted, it could be hypothesized that drug-induced bioelectrical changes on unimodal sensory association cortex may have played a role in the modality-specific modifications in the visual, somatic and auditory perception reported by the volunteers. Additionally, it appears

reasonable to assume that effects on transmodal brain areas could account for more complex cognitive modifications which also characterize the subjective experience elicited by *ayahuasca*. In this respect, the temporo-parietal and frontomedial heteromodal association cortex, the cingulate and the temporomedial cortices play relevant roles in the neurobiology of attention, emotion, and memory (Devinsky et al., 1995; Nyberg et al., 1996; Squire and Zola-Morgan, 1991). Clearly, additional studies of *ayahuasca* and other psychoactive drugs by means of LORETA are warranted. Comparison of the LORETA results with data from nuclear medicine techniques are also indicated. In contrast with the widespread power density decreases we observed for *ayahuasca* in posterior regions with LORETA, PET and SPECT studies of acute mescaline and psilocybin administration have shown blood flow and metabolic increases in the frontal cortex (Gouzoulis-Mayfrank et al., 1999a; Hermle et al., 1992; Vollenweider et al., 1997).

At the doses administered, *ayahuasca* induced a different pattern of effects on PPI and P50. The results obtained seemingly indicate no effect, or at best, a mild enhancing effect of the drug on PPI, a measure of sensorimotor gating. In the only other human study performed to date involving serotonergic psychedelics, the administration of psilocybin provoked a significant increase of PPI at a prepulse-to-pulse interval of 100 ms, with no significant effects on habituation (Gouzoulis et al., 1998). Interestingly, the pattern of effects exerted by serotonergic drugs on the human PPI in the limited number of studies conducted is opposed to that by dopaminergic/noradrenergic agonists. Thus, *d*-amphetamine and bromocriptine have been shown to impair PPI in healthy volunteers (Abduljawad et al., 1998; Abduljawad et al., 1999; Hutchison and Swift, 1999). On the contrary, the significant dose-dependent decreases in P50 suppression after *ayahuasca* suggest a suppressing effect of the drug on normal sensory gating in humans. To our knowledge, P50 suppression has not been assessed previously in humans following the administration of a 5-HT_{2A/2C} agonist. The only studies that have evaluated the effects of pharmacological challenge on this measure in humans have concentrated mainly on catecholaminergic drugs. Both *d*-amphetamine and the α_2 -adrenoceptor antagonist, yohimbine have thus been shown to impair P50 suppression in healthy volunteers (Adler et al., 1994a; Light et al., 1999). Furthermore, the dopamine agonist bromocriptine has also been found to disrupt P50 suppression (Adler et al., 1994b) in humans. The pharmacological characteristics of the beverage, which combines MAO-

inhibitors and DMT, precludes the generalization of the present findings to all 5-HT_{2A/2C} agonists. Results in the present study should therefore be regarded with caution and should be replicated using wider dose ranges.

The time course of DMT plasma concentrations closely paralleled that of subjective effects, with peak DMT concentrations and peak effects obtained between 1.5 and 2 h. It is worth noting the small percentage of DMT which apparently reaches systemic circulation after *ayahuasca* administration. Based on Strassman's i.v. data, our calculations yield a bioavailability of only 10-15% for DMT in *ayahuasca*. An analogous value is obtained performing the calculations with the apparent volume of distribution reported by Callaway and coworkers (1999). In fact, the above bioavailability figure may be overestimated. In their study, Strassman et al. (1994) draw the first blood sample two min after the end of the DMT bolus. Thus, the maximum plasma concentration –which is obtained immediately after completion of the i.v. bolus– was missed. Greater DMT plasma levels after i.v. administration would have led to a smaller volume of distribution value and this in turn to a smaller bioavailability for DMT in *ayahuasca*. The role of the β -carbolines on DMT clearance deserves further analysis. 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 non-linear increment of DMT levels following the administration of increasing doses of *ayahuasca* and could be due to the action of the higher amounts of β -carbolines administered. In line with this possibility, while Callaway and coworkers found an apparent volume of distribution value for DMT similar to that in the present study, they reported higher half-life and lower clearance values. The role of the β -carbolines in the possible non-linearity of DMT levels between *ayahuasca* doses could be addressed in a repeated administration study.

The absence of measurable levels of plasma harmine suggests efficacious metabolism of this alkaloid. The rapid turnover of harmine to harmol has been observed in vitro (Yu et al., 2003). Phenotyping or genotyping volunteers for the CYPs involved in harmine O-demethylation could shed some light on the differences observed between our sample and that of Callaway and coworkers (1999), where measurable levels of harmine were found in plasma.

In the present investigation we could not demonstrate a clear-cut MAO inhibition by measuring urinary monoamine metabolite levels. This may have been related to the β -carboline amounts administered with the *ayahuasca* doses. These were established in terms of administered DMT per kg body weight. At the 0.85 mg DMT/kg dose which was used in the final study as the high dose, volunteers received 1.45 mg/kg harmine. This value is slightly below the 1.5 mg/kg found by Ott (1999) to be the threshold dose necessary to render DMT orally active in self-experiments. Although 1.45 mg/kg may have been sufficient to allow sufficient DMT to reach undegraded systemic circulation and to elicit psychotropic effects, it may not have been enough to modify the profile of endogenous monoamine metabolites in urine. The assessment of the in vivo MAO inhibition effect with this methodology may render positive results employing *ayahuasca* batches with higher β -carboline amounts. Alternatively, a repeated dose administration study could possibly yield a greater degree of MAO inhibition.

Increases in SBP, DBP and HR did not appear to be a robust effect of *ayahuasca*. While a tendency was found for SBP increases in the pilot study, this variable was not found to be affected in the final study. Instead, increments in DBP reached statistical significance, although the magnitude of the effect was only moderate. The small sample of the pilot study (only 5 volunteers) may have been insufficient to demonstrate the cardiovascular effects of *ayahuasca*. Both in the pilot and final studies, increases in SBP, DBP and HR were milder than those reported for other more prototypical sympathomimetics, such as amphetamine or MDMA, at doses showing psychotropic properties (de la Torre et al., 2000; Mas et al., 1999). The use of positive controls in future studies on the cardiovascular effects of *ayahuasca* is also indicated.

CONCLUSIONS

1. The psychotropic effects of *ayahuasca* vs. placebo were demonstrated by means of structured self-assessment instruments both in naive and in experienced *ayahuasca* users. The tea induces dose-dependent changes in the perceptual, affective, cognitive and somatic spheres, with a combination of stimulatory and psychedelic effects. The overall experience is of longer duration and milder intensity than that previously reported for intravenously administered DMT.
2. The central effects of *ayahuasca* were objectively measured by means of q-EEG, showing a time pattern which closely paralleled that of subjective effects. Results in the individual q-EEG variables are in line with those previously described for other serotonergic psychedelics and share some features with the profile of effects shown by pro-serotonergic and pro-dopaminergic drugs.
3. The use of the LORETA source location technique identified the EEG power decreases over somatosensory, auditory and visual association cortices, over temporo-parietal heteromodal association cortex and in paralimbic structures with relevant roles in emotion and memory processes. These areas may be involved in the psychological effects elicited by *ayahuasca*.
4. Diverging effects are observed on each of the two gating measures evaluated. While a decremental effect of *ayahuasca* on sensory gating was found, no distinct effects were observed on sensorimotor gating.
5. Following the oral administration of *ayahuasca*, measurable plasma levels were observed for DMT, harmaline and THH. Based on the calculated bioavailability, only a small percentage of the total DMT in *ayahuasca* appears to reach systemic circulation. The time course of DMT plasma concentrations parallels the evolution of subjective effects, with peak plasma concentrations and peak subjective effects attained at 1.5 h. While harmine was not found in plasma except for a few time points in four of eighteen volunteers, all volunteers showed measurable levels of harmol and harmalol, the *O*-demethylated analogues of harmine and harmaline. Results suggest an intense first-pass metabolism for harmine.

6. In vivo MAO inhibition following *ayahuasca* administration could not be firmly and definitely established measuring the excretion of urinary monoamine metabolites. While *ayahuasca* increased normetanefrine excretion in line with the hypothesis, the levels of the MAO-dependent metabolites did not show the decreases expected for a MAO inhibitor.

7. *Ayahuasca*-induced increases in cardiovascular measures were moderate and statistical significance could only be demonstrated for DBP. The drug exerts a series of unpleasant somatic-dysphoric effects, the most common of which are altered physical sensations and nausea. However, in contrast with reports from field observations, *ayahuasca*-induced vomiting was infrequent. Transient disorientation and anxiety experienced by one volunteer was the most disturbing adverse event observed.

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