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Ayahoasca: an experimental psychosis that mirrors the transmethylation hypothesis of schizophrenia

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Abstract

The experimental psychosis observed after drinking Ayahoasca, a South American hallucinogenic beverage from the Amazon Indians, reproduces the pathologic transmethylation theory of schizophrenia. This theory postulates a decrease in the monoamine oxidase (MAO) activity, which results in the accumulation of methylated indolealkylamines, such as bufotenin (5-hydroxy-*N*,*N*-dimethyltryptamine), *N*,*N*-dimethyltryptamine (DMT) and 5-methoxy-*N*,*N*-dimethyltryptamine. These substances are strong hallucinogens as has been previously confirmed experimentally. On the other hand, it is known that Ayahoasca is a beverage usually prepared by boiling two plants, one of them rich in β-carbolines, which are naturally occurring strong inhibitors of MAO, and the other with high quantities of DMT. This particular combination reproduces what is supposed to occur under pathologic conditions of different psychoses. The effects of Ayahoasca were studied in subjects, assessing urine levels of DMT by gas chromatography-mass spectrometry (GC-MS) before and after the intake of the beverage. The results of this study confirm that the hallucinogenic compounds detected in the healthy subjects' (post-Hoasca, but not before) urine samples are the same as those found in samples from acute psychotic unmedicated patients. The chemical composition of the Ayahoasca beverage, and of the plant material used for its preparation are also reported as well as psychometric and neuroendocrine subject parameters.

Keywords: Ayahoasca; Methylated indolalkylamines; Psychodisleptic; Gas chromatography-mass spectrometry; Transmethylation hypothesis; MAO; Schizophrenia

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1. Introduction

Transmethylation hypothesis of schizophrenia (Stam et al., 1969; Smythies, 1983) proposes that, due to enzymatic disturbances (Buscaíno et al., 1966, 1969), schizophrenic patients produce high amounts of methylated indolealkylamines, such as bufotenin (5-hydroxy-*N*,*N*-dimethyltryptamine) (Fuller et al., 1994), 5-methoxy-*N*,*N*-dimethyltryptamine and *N*,*N*-dimethyltryptamine (DMT) (Friedhoff and Van Winkle, 1964; Fischer et al., 1971; Ciprian-Ollivier et al., 1986), which are strong hallucinogenic compounds for healthy subjects. These substances are preferential substrates for monoamine oxidase (MAO), in a way that when a high single dose is given, 30 min later only 1% can be recovered from blood and/or urine samples (Hryhorczuk et al., 1986; Sitaram and McLeod, 1990). In spite of this high turn-over, methylated indolealkylamines have been reported in urine samples from psychiatric patients, not only schizophrenics (Tanimukai et al., 1970; Saavedra and Axelrod, 1972; Strahilevitz et al., 1975). In our previous work (Ciprian-Ollivier et al., 1986, 1988; Ciprian-Ollivier, 1991), in agreement with other authors (Rodnight et al., 1978; Murray et al., 1979; Checkley et al., 1980), it has been proposed that these compounds are related to perceptual disturbances, remarking that not only true hallucinations but more subtle perceptual disturbances are present in several entities. Therefore, methylated indolealkylamines may play the role of 'state markers' for clinical or subclinical psychoses rather than being a trait of any diagnostic category. Their accumulation in patients could be caused either by an acceleration in the kinetics of their production or, and most probably, by a decrease in the kinetics of the enzyme (MAO) responsible for the breakdown of the methylated indolealkylamines (Mc Geer et al., 1978; Räisänen and Kärkkäinen, 1978, 1979). Many reports are known of decreased MAO activity in schizophrenia, which are thus in agreement with this theory (Davis et al., 1982). Decreased MAO activity allows the accumulation of indolealkylamines, crossing the blood brain barrier (BBB) and acting on the central nervous system (CNS), due to the fact that these compounds are not necessarily produced within CNS.

In the South American Amazon Basin a hallucinogenic beverage is used by shamans to induce mystic states that clearly mirrors this situation. Ayahoasca or Hoasca tea (the Brazilian name for Ayahuasca; see Section 1.1) is essentially made by boiling two plants, *Banisteriopsis caapi* and *Psychotria viridis*. The first is rich in β-carbolines derivatives, which are strong natural MAO inhibitors, and the second contains high amounts of DMT, being an important natural source of this compound (Rivier and Lindgren, 1972; McKenna et al., 1984; McKenna and Towers, 1985; McKenna et al., 1986). In an empirical way, Amazon shamans discovered, many years ago, that in order to have the hallucinogenic effect of one of the plants, *Psychotria* sp., the presence of the other, *B. caapi*, was needed. Therefore, peripheral MAO inhibition by β-carbolines allows the concentration of DMT and further BBB crossing, thus exerting their hallucinogenic effects in the CNS.

In this paper, we studied several biological effects of Ayahoasca or Hoasca tea in order to evaluate the ability of this beverage to modulate serotonergic receptors, and through these results, to determine to what extent cortisol, prolactin and serotonin levels as well as perceptual and cognitive processes are affected. As is known, recent basic research with radioligands showed outstanding differences in the anatomical distribution of the 5-HT receptors in rat and human brain, and therefore, human research is necessary as an ethnopharmacological contribution to the effects due to Hoasca intake. Furthermore, the occurrence of DMT in Ayahoasca or Hoasca tea and in the urine samples from the subjects confirm that the reported biological and cognitive effects are produced by these methylated indolealkylamines assisted by the β-carboline derivatives.

1.1. Ethnobotany of Ayahoasca

South American psychoactive drinks and snuffs used by the indian tribes for shamanic, medicinal and/or religious ceremonial purposes have been extensively reviewed and studied by ethnobotanical explorers, botanists, chemists, anthropologists and pharmacologists (Schultes, 1954, 1957, 1968;

Ríos, 1962; Biocca et al., 1964; Marini-Bettolo et al., 1964; Efron et al., 1967; Schultes et al., 1969; Flores and Lewis, 1978; Schultes, 1985). Furthermore, a variety of other plants and fungi containing hallucinogenic substances has been used as constituents of medicinal, ritual and recreational drinks and snuffs, also in relation to religious practices in ancient and contemporary aboriginal South American groups (Schultes, 1967a,b, 1969a,b, 1972; Lewis and Elvin-Lewis, 1977; Schultes, 1977; Schultes and Hofmann, 1980).

The first european references of the Ayahoasca beverage or Ayahuasca drink (aya-huasca, means dead man's vine, vine of the dead or vine of the souls, in quechua, the language of the ancient Incan Empire) are due to missionary jesuits, thus Pablo Maroni in 1737 described it as a narcotic drink, and Magnin (1740) its use as a medicinal plant by the Maynas Indians, thus suggesting that the same name was used for both the drink and the plant. Primitive cultures considered the vessels for drinking Ayahuasca or other psychedelic drinks as sacred, and consequently, artistic coloured objects were designed with mythological figures or subjects, or sacred animals, which are carefully kept in Ethnographical Museums of Perú, Ecuador, Colombia and other countries with a rich precolumbian culture. Therefore, through archeological research it is possible to follow the precolumbian evolution of the sacred plants in the different ecological systems of this region, as well as the folk-preparation, ritual consumption and erotic effects. Thus, collective ceremonies used large bowls, from which each member swallowed the ritual liqueur in turn. In contrast, in healing ceremonies or cure rituals only the shaman or tribe medicine-man in a special house drank the sacred brew in a small pot (Naranjo, 1986). Antique ceramics of these small vessels come from the Sangay stage (2400 b.c.) in Ecuador (Naranjo, 1986). A variety of metallic cooking pottery, particularly the so-called 'ollas de brujo' for making the Ayahuasca potion, was also found in the littoral region of Ecuador from the evolved Milagro-Quevedo culture (500–1500 a.c.) with a sophisticated agriculture and metallurgical knowledge including the use of gold and copper. Two ethnical groups, the Colorados and the Cayapas, who live in this region, maintain the shaman use of the Ayahuasca extract under the name 'pinde' or 'pilde', and 'nepi', respectively (Naranjo, 1986).

In postcolumbian times the mestizo populations continued the ritual and ethnomedicinal uses of the Ayahuasca potions, but unfortunately some reports of explorers and investigators were somewhat confused, probably due to the different aboriginal names in the tribal languages given to the potions, plants and admixtures. In addition, each tribe has its own name for the same plant. For example, in Ecuador, Ayahuasca is known as 'yajé' in the north, 'mii' for the Aucas and 'natema' for the Shuar (Naranjo, 1979). Richard Spruce, who lived closely with the native Amazonian people, gave detailed, amusing and pioneer information in english on the malpighiaceous narcotic, first described the *caapi* liana, now called *B. caapi* (Spr. ex Griseb.) Morton (Malpighiaceae), and witnessed its use among the Tukanoan Indians of the Vaupés river of Brazil in 1852 (Schultes, 1968; Pinkley, 1969).

The forest liana *B. caapi* grows spontaneously in an extensive area of the Orinoco and Amazon Basin, including Venezuela, Colombia, Ecuador, Perú, Bolivia, and Brazil, in the rain forest and jungle, with high humidity. In the littoral region of Ecuador there is another area of Ayahuasca, western Quito, on the other side of the Andes mountains (Naranjo, 1979).

Even though the amazonian Ayahuasca beverage occasionally contains only the bark of the jungle liana *B. caapi* or *Banisteriopsis inebrians* (Malpighiaceae), which contain β-carbolines, it is often a complex narcotic due to the addition of other plants (admixture or mixture, 'chacruna' in quechua) (Schultes, 1972). Del Castillo (1962) described the chacruna as *Psychotria* spp. (Rubiaceae). However, Borman, a missionary-linguist reported that both the malpighiaceous *Banisteriopsis rusbyana* (now known as *Diplopterys cabrerana*) and the rubiaceous *Psychotria psychotriaefolia* (Seem.) Standl., a relative of *P. viridis*, were added to the 'yajé' drink prepared from *B. caapi* in order to increase and intensify the visions (Schultes, 1969b). Other *Psychotria* spp. from northwestern Amazon were

detailed by Schultes (1985). Maximum hallucinogenic effect is obtained with leaves of *Psychotria carthagenensis* Jacq., *P. viridis* Ruiz et Pavon (Rubiaceae), or the malpighiaceous jungle liana *D. cabrerana* (Cuatrecasas) Gates (formerly known as *B. rusbyana*) (Gates, 1979, 1982), all of which contain as major component DMT. *P. carthagenensis* is also a Maya medicinal plant against toothache (Arnason et al., 1980). Amazon Kofán Indians of eastern Ecuador and Colombia used *Banisteriopsis* and small rubiaceous fruits from the plant called 'o-pri-to', the same name by which they refer to the 'heavenly people' with whom they commune during the 'yajé' intoxication (Pinkley, 1969). The Cashinahua call the admixture 'kawa', while the Culina Peruvian Indians 'appane', and the Sharanahua Indians, linguistically related to the Cashinahuas, also called the plant 'kawa'. These tribes of the Purús river in Loreto, Perú also recognized, like the Cashinahua, different kinds of this rubiaceous additive (Rivier and Lindgren, 1972; Rüf, 1972). The collection of admixtures with voucher specimens and the aboriginal name, obtained by Rivier and Rüf from these two ethnic groups on the Purús river is the largest from a specific group of indians (Pinkley, 1969; Rivier and Lindgren, 1972; Rüf, 1972).

Other occasional additives used particularly in Peruvian Amazon include leaves from Apocynaceae (*Tabernaemontana* spp.), Solanaceae, Acanthaceae, and many others such as cacti, mints, sedges, and ferns (Schultes, 1969b, 1972, 1985; Pinkley, 1969; Rivier and Lindgren, 1972; McKenna et al., 1984; McKenna and Towers, 1985; McKenna et al., 1986). The solanaceous genera include *Nicotiana* sp., *Brugmansia* sp. and *Brunfelsia* sp., which contain alkaloids, such as nicotine, scopolamine, and atropine, which additionally affect both central and peripheral adrenergic and cholinergic neurotransmission. The admixture selected depends on the magical, medical or ritual use, e.g. *Toe negra* in Amazonian Perú (*Teliostachya lanceolata* var. *crispa*, family Acanthaceae), is cultivated for use alone as a narcotic and as an additive to Ayahuasca (*B. caapi*). When used alone the boiling of ten leaves for 7 h results in the loss of sight for 3 days, during which time conversation with the spirit of the plant is possible. The plant *Juanulloa ochracea* (Solanaceae), which contains the alkaloid parquina is called Ayahuasca in the Colombian Putumayo, and is added to *Banisteriopsis* drinks. Also the Colombian Vaupés, use *Sabicea amazonensis* (Rubiaceae) leaves to make the drink sweet instead of bitter.

One investigator of medical practices amongst the Siona Indians of the Colombian Putumayo, who are known as having a rich ethnopharmacopoea, reported that these natives recognize 17 different classes of yajé and that each of these admixtures gives a different kind of vision (Rocha, 1905; Schultes, 1968; Reichel-Dolmatoff, 1970; Schultes, 1972). Also the Barasana Indians of the Piraparana river of Colombia know 29 varieties. Some of these names may be alternate names for the same plant, others may represent age or ecological forms of *B. caapi*, but some undoubtedly refer to different plants that are used as admixtures.

Several tribes of the Peruvian Amazon used Ayahuasca for healing, ritual aspects being more strongly marked in tribal usage (Delgado et al., 1972) in other regions where its use is more widely for magic objectives, as in the Ecuadorian Amazon (Villavicencio, 1858), where the sundry tribes of the upper Napo river use Ayahuasca for sorcery, witchcraft, prophecy and divination. Moreover, ethnic groups of south and middle Ecuador use the drug as a concentrated extract, while the Tucanos from Colombia use a diluted extract.

Therefore, the drug practice dates to precolumbian times, and a short time after the Spanish conquest, Ayahuasca was integrated into the ethnomedical traditions of the mixed populations (european plus aborigines) called mestizos. Nowadays the drug is important in ethnomedicine and shamanism in indigenous mestizo populations of the Amazonian region for healing, for divination and as a magical tool for the supernatural realm (Dobkin de Ríos, 1970, 1972; Luna, 1984). Although little is known of the medicinal properties of the hallucinogenic plants, reports by Schultes and other ethnobotanists who have participated in the drinking of the hallucinogenic potions, suggest that a variety of physiological effects ac-

companied the hallucinogenic experience, the most common being vomiting and diarrhea. During native ceremonies, repeated references are also made to the cleansing (emesis) and purifying properties of these drugs. Since parasitic helminthic and protozoal infestations of the gastrointestinal tract are prevalent throughout the tropics, and especially in the Amazon basin protozoal diseases, such as malaria, leishmaniasis, Chagas disease, various trypanosomiasis and toxoplasmosis, shamans and medicinal tribe men (hechiceros) select alkaloid-containing plants which cure by expelling the parasites, e.g. hallucinogenic isoquinoline and tryptamine-related plant alkaloids are known as powerful emetics, and as antimicrobials and anthelmintics. Consequently, Cavin developed an in vitro chemical screening test to determine the effects of various alkaloids against *Trypanosoma cruzii* (Chagas disease) epimastigote forms. Harmine, quinine hydrochloride, vinoblastine sulfate, emetine dihydrochloride and atropine showed marked effects (over 70% inhibition after 96 h), while arecoline and berberine, which are employed as anthelmintics, showed 40% inhibition after 96 h (Rodríguez et al., 1982). Psychoactive alkaloids are effective antagonists of the neuromuscular system of helminths, inhibit protozoan parasites and were selected by Amazonian people for their medicinal value and also incorporated into religious ceremonies (Rodríguez et al., 1982). Aboriginal groups and especially shamans correlated the psychotropic effects of these alkaloids and the alleviation of symptoms caused by parasitic worms and protozoans and thus used the former as a dosage indicator. They incorporated these plants into religious ceremonies using psychoactivity as an effective dose marker (Rodríguez et al., 1982), and included this knowledge in the shamans' education. The borrachera yagé potion prepared by the witch for medicinal purposes is usually a dreadful-tasting, reddish-coloured decoction as reported by Rodríguez et al. (1982) when drinking it with the Kamsa Indians of the Upper Putumayo in Colombia. After ingestion, they experienced no hallucinogenic effect, but violent vomiting and diarrhea. The potion was prepared from the bark of the vine *B. caapi*, without any admixture.

Banisteriopsis species are not usual in Argentina (O'Donell and Lourteig, 1943; Dawson, 1965; Rossow, 1988), but one of the species found is *B. nitrosiodora* Griseb., which is practically devoid of alkaloids (Deulofeu, 1967a,b). In fact, the hallucinogenic drink is not used in Argentina. Instead, other tryptamine-containing species of the genus *Piptadenia* (Leguminosae) grow in northwestern Argentina, and were used in hallucinogenic snuffs by the Lules Indians of the western Chaco, and also in ritual ceremonies of the Matakos Indians (Deulofeu, 1967b). The chemical components were studied in our country by Iacobucci and Rúveda (1964).

In Brazil, instead, the hallucinogenic beverage Ayahoasca has an aboriginal as well as a cult-use.The Kachinaua tribes of Brazil prepare the hallucinogenic drink directly from *Banisteriopsis tastevinii* (Schultes, 1972). During Spruce's fieldwork on the upper Negro river of Brazil and adjacent Colombia and Venezuela, the Tukanoan Indians used '*caapi*' (Tupi name for 'grass' or 'thin leaf' in Brazil) to obtain visual hallucinations and a feeling of bravery. Also the primative Guahibo Indians along the Orinoco at the Cataracts of Maypures used '*caapi*' as a drink and also chewed the dried stem. These tribes use it in a traditional medical use, reserved for the witch-medicinal man or shaman, who takes the drug and interprets the visions in order to detect the cause of illness. In addition to this therapeutic use of the drug, there is also a social one in order to have visions (Ducke, 1958; Schultes, 1985).

From Amazonian Brazil Prance (1970) reported the preparation and use of the drink not only by aboriginal groups but also by the Brazilian townsmen who belong to a cult centered around Ayahuasca (called cipó, Ayahoasca, Hoasca tea, Daime). The vine of *Banisteriopsis* is cut into pieces and boiled in a saucepan of water, the leaves of *Psychotria* are added at this point and the mixture is further boiled for ca. 30 min. The dark brown liquid is cooled and may be bottled and corked to be consumed at home for up to 4 weeks. Families use the beverage without apparent harm or addiction and individuals used to gather for large drinking bouts. Always there is a person who does not drink in order to prevent

bad hallucinating experiences in new consumers and to control the progression of the visions. The members shut their eyes and wait for the visions after drinking. Detailed experiences have been previously reported (Prance, 1970; Lewis and Elvin-Lewis, 1977), showing an increase of communication and extrasensory perception beyond usual conscious levels.

Nowadays, several brazilian syncretic religious movements are based on the ritual use of Ayahoasca, e.g. União do Vegetal, that are described in this paper.

1.2. Chemistry and mechanism of action

Harmine was detected in the material sent by Spruce from Brazil in 1852 and analysed in 1968 (Schultes et al., 1969) and earlier (Chen and Chen, 1939) in the stem, leaves and roots of an authentic sample of *B. caapi*. Harmine, harmaline and (+)-THH were reported from *B. caapi* and *Prestonia amazonicum* (Hochstein and Paradies, 1957).

The chemical composition of the South American *Banisteriopsis* species was analysed in Argentina, in our Department of Organic Chemistry by Deulofeu (1967a), who described harmala alkaloids. Also, Cassels from our Department described the healing practice, botany and chemistry from the Peruvian Ayahuasca (Delgado et al., 1972). The psychotropic properties of these alkaloids and the so-called harmaline syndrome was described by Naranjo (1967), who carried out electrophysiological studies on cats.

DMT was reported in *B. rusbyana* (now *D. cabrerana*), harmine and harmaline in *Banisteriopsis* spp. (Der Marderosian et al., 1968; Agurell et al., 1968a,b, 1969), as well as DMT and other non-indole alkaloids from leaves of *P. viridis* (Der Marderosian et al., 1970). In the same study, another *Psychotria* was reported to contain DMT only, while a third specimen of *Psychotria* leaves was totally devoid of alkaloids. The indians mixed all three of these *Psychotria* species with Ayahuasca, according to Pinkley (1969).

Rivier and Lindgren (1972) identified substantial amounts of DMT and traces of *N*-methyltryptamine (MMT) and 2-methyl-1,2,3,4-tetrahydro-β-carboline (MTHC) in the leaves of *P. viridis*, and when DMT was not present, they found instead MMT and MTHC. These authors also found that *P. carthaginensis* contains a larger amount of alkaloids than *P. viridis*, practically all DMT and that other species of *Psychotria* (*P. emetica*, *P. bacteriophylla* and *P. undulata*) were devoid of indoles and β-carbolines. Trace amounts (0.007–0.0001%) of another six β-carbolines (harmic amide, acetyl norharmine, ketotetrahydronorharmine, harmine *N*-oxide, harmic acid methyl ester and harmalinic acid) have been also reported (Hashimoto and Kawanishi, 1975, 1976) in addition to the three main constituents as well as the pyrrolidine orchideaceous alkaloids shihunine and dihydroshihunine from *B. caapi* (Kawanishi et al., 1982). McKenna et al. (1984) analysed the components of admixtures, the alkaloids of Ayahuasca from Perú, alkaloid content variations in several *B. caapi* cultivars and also, three admixture plants were screened for alkaloids. These authors reported that the Ayahuasqueros of Perú recognized several different 'kinds' of Ayahuasca, which varied in their psychological effect based in part on the type of admixture plants, and in part on the type of *B. caapi* (e.g. 'cielo','lucero', 'rumi'; as many as ten kinds of *Banisteriopsis* vine), probably different cultivars, races, or chemical or morphological varieties. However there were no outstanding morphological differences between the three or four kinds of *B. caapi* collected, but considerable alkaloid content variation between the samples. The variations observed may be due to the age of the plant, and/or environmental conditions (soil, light, water) affecting each plant growth. McKenna et al. (1984) found alkaloid amounts similar to those of Rivier and Lindgren (1972), and identified DMT as the single major base (1–1.6 mg/g dry wt), and sometimes only traces of MTHC in the leaves of *P. viridis* from Perú, but no alkaloids in its fruits or stems. No alkaloids were found in the *P. carthaginensis*, used by one ayahuasquero. The occurrence of tiny dolmatia-like structures (espinas) were pointed out by the Ayahuasqueros as the key feature to identify good *Psychotria* from false chacrunas (McKenna et al., 1984). In fact, the colleter types and the

relationship to the bacterial leaf nodule symbiosis is very important in the systematics of Rubiaceae (Lersten, 1975).

D. cabrerana (the malpighiaceous admixture; 'chagro-panga' or 'ocoyage') gave DMT (1.74 mg/g dry wt) and an extremely trace amount of 5-OH-DMT by GC-MS, usual admixture in southern Colombia and Ecuador (Pinkley, 1969). Indole oligomers, polyindoline alkaloids and pyrrolidinoindolines, such as psycholeine, hodgkinsine, calycanthidin, quadrigemine, psychotridine, isopsychotridine, and other tetramer and pentamer related compounds have been also isolated from *Psychotria* spp. (Libot et al., 1987; Guéritte-Voegelein et al., 1992). It is interesting to note the outstanding accumulation of Ni in some *Psychotria* species (1.8–4.7% Ni in leaves of *P. douarrei* from New Caledonian), and the fact that *P. baillonii* only grows in extremely alkaline soils (Ni-tolerant ecotypes) (Hegnauer, 1990).

Only a few chemical analyses of the narcotic beverage have previously been carried out (Clinquart, 1926; Rouhier, 1926; Chen and Chen, 1939; Rivier and Lindgren, 1972; McKenna et al., 1984). Hochstein and Paradies (1957) found harmine, harmaline and tetrahydroharmine (THH) in the aqueous extract used by the natives and that the concentration of harmaline and THH were greater than in the plant. Der Marderosian et al. (1970) isolated DMT, much harmaline and a little harmine from 'nixipae' of Cashinahua (stem of *Banisteriopsis* sp. and the leaves of two not completely identified species of *Psychotria*).

One of the most complete studies of the plants and drink is due to Rivier and Lindgren (1972), who identified harmine, harmaline, THH, harmol and 6-methoxytryptamine in *B. caapi* (GC-MS) and DMT, MMT and MTHC in *P. viridis* and *P. carthagenensis* (vide supra). They also analysed the drink, called Ayahuasca in Perú identifying harmine, harmaline, THH and DMT, and quantified the alkaloids administered in the drink. The indians distinguished three kinds of the vine (*B. caapi*): red, black and white, based more in the colour of the drink than on the plant morphology. The Peruvian mestizos made no distinction between the red and the white drink, knowing only black and white. In this whole region the stems of *Banisteriopsis* sp. were always blended with the leaves of *Psychotria* sp.. The Sharanahua distinguished at least two kinds of *Psychotria*, and the Culina two species of *Psychotria*, too. Other plants are sometimes added to or taken together with the beverage, such as *Opuntia* sp. (Cactaceae), *Datura* sp. (probably *D. suaveolens*) (Solanaceae) and *Nicotiana* sp. (Solanaceae). Customarily, the indians smoke all night long, when taking the Ayahuasca drink (Rivier and Lindgren, 1972).

McKenna et al. (1984) also studied Ayahuasca brews obtained from Ayahuasqueros of the Peruvian towns of Iquitos, Pucallpa and Tarapoto. Harmine, harmol, harmaline and THH were the major β-carbolines in all the samples, while harmalol was not detected in any sample except one. DMT was found in all the samples in one from Tarapoto prepared with *P. carthagenensis* instead of *P. viridis*. The sample from Pucallpa had the highest total alkaloid content: 75.7 mg/g dry wt of which 76% was harmine, 10.6% was THH, and 7.6% was DMT. Both regions used different methods of preparation. Purús: 1h-boiling, while Pucallpa ca. 10–15 h, adding fresh water, filtering and further concentrating.

The mechanism of action earlier suggested (Efron et al., 1967; Schulgin, 1976) to explain the oral hallucinogenic activity of the Ayahuasca drink is based on the fact that the β-carbolines of *B. caapi* are highly active reversible inhibitors of MAO (Udenfriend et al., 1958; McIsaac and Estevez, 1966; Buckholtz and Boggan, 1977), and consequently prevent DMT deamination by visceral MAO, thus transforming the potent hallucinogen DMT present in the *Psychotria* spp. into an orally active compound. In fact, DMT is known to be inactive orally (Schulgin, 1976) due to degradation by intestinal and hepatic MAO.

The fully aromatic β-carbolines are the most effective MAO inhibitors, and the activity decreased with increasing saturation of the piperidine ring, tetrahydro-β-carbolines still showing

significant activity (Udenfriend et al., 1958). Experiments by Fuller et al. (1970) showed that harmaline selectively inhibited oxidation of serotonin, indicating that it was a specific inhibitor of MAO-A. However, the first empirical demonstration of the effect of Ayahuasca drink on MAO was due to McKenna et al. (1984), who screened in vitro various β-carbolines, mixtures of β-carbolines and Ayahuasca drinks for activity as MAO inhibitors, and compared structure–activity relationships in assays using rat-liver as the source of MAO and 5-hydroxy [side-chain-2-^{14}C]-tryptamine creatinine sulphate as substrate. The degree of Ayahuasca drink MAO inhibition was directly correlated in vitro with the concentration of MAO-inhibiting β-carbolines. Thus, one Ayahuasca sample (3.5 mg/ml total alkaloids) still showed $>40\%$ inhibition of the enzyme at 10^{-5} full strength ($I_{50} = 1.58 \times 10^{-5}$ M), while a second Ayahuasca sample (4.8 mg/ml total alkaloids) exceeded 50% inhibition even at one ten-millionth (10^{-7}) ($I_{50} < 1.0 \times 10^{-7}$ M) the concentration of the undiluted brew. Inhibition experiments using mixtures of β-carbolines further indicated that their effects in combination are additive, rather than synergistic or antagonistic (McKenna et al., 1984). The I_{50} (3.16×10^{-7} M) of an equimolar mixture of harmine + harmaline + THH (1:1:1) is ca. intermediate between the I_{50} value of the most active constituent of the mixture (harmaline, $I_{50} = 1.58 \times 10^{-8}$ M) and the least active (THH, $I_{50} = 1.77 \times 10^{-6}$ M), thus indicating that these compounds do not interact synergistically with respect to their inhibition of MAO. The Ayahuasca 'analogue' (69% harmine + 26% THH + 4.6% harmaline, with a similar composition to one of the Ayahuasca samples) showed I_{50} values nearly identical with those of the equimolar mixture (3.98×10^{-7} M and 3.16×10^{-7} M, respectively) indicating that the combination of harmine and THH alone can account for most of the MAO inhibition exhibited by Ayahuasca. Although harmaline is equivalent to or slightly stronger than harmine as MAO inhibitor, none or only traces in Ayahuasca are required because it does not contribute significantly to the MAO inhibition described (McKenna et al., 1984).

2. Materials and methods

2.1. Plant material and Ayahoasca samples

The botanical material and Hoasca teas were obtained from Brazil, 'União do Vegetal' (UDV) ('Santo Daime') with the consent of the President of the Scientific Studies Society.

The plant material consisted of two different species used for the preparation of the hallucinogenic beverage: the stems of *B. caapi* (Spruce ex Griseb.) Morton (Malpighiaceae) and the leaves of *P. viridis* Ruiz et Pavon (Rubiaceae). It was dried at room temperature in the air without exposure to the sun to prevent any photochemical degradation and/or transformation. Moreover, according to the ayahuasqueros sun exposure may destroy the effects of the tea.

Voucher specimens of *B. caapi* and *P. viridis* were deposited in the Herbarium of the Laboratorio de Plantas Vasculares, Departamento de Ciencias Biológicas, Facultad de Ciencias Exactas y Naturales, Universidad de Buenos Aires, and identified by Professor Dr Ramón Palacios and Dr Enrique M. Zallocchi.

Hoasca tea samples were carried refrigerated from Brazil to Argentina. They were prepared by the respective Brazilian cult-groups in the traditional long procedure, by boiling a mixture of *B. caapi* and *P. viridis*. Dark green-brownish dense liquids were obtained.

The tea samples were administered at a standardized dose based on the previous experience of usual users, ca. 100 ml.

2.2. Extraction of the alkaloids

The alkaloids were obtained separately from the stems of the liana *B. caapi* and the leaves of *P. viridis* according to the following procedure. Powdered plant material was ground in a mortar for about 1 min with 10% ammonia solution, then mixed with basic aluminiun oxide (activity I). The mixture was packed loosely into a glass column (20 cm long by 1.5 cm in diameter), and the alkaloidal bases were eluted with methylene chloride. The column was monitored by TLC (silica gel). The first 5 ml of eluate were col-

lected, concentrated in vacuo and then chromatographed (Wagner et al., 1984). DMT synthesized in our laboratories, as well as harmine and harmaline (Sigma) were used as standards.

All extracts were examined by TLC and HPTLC, on silica gel GF_{254} glass-backed precoated plates and CH_2Cl_2–EtOH–28% NH_4OH (85:14:1, v/v/v) as solvent and the spots were visualized by spraying with Dragendorff's reagent.

The alkaloids were also analysed in urine samples of the volunteers and controls. Test 24-h urine specimens, including the first void of the day, were kept in dark well-closed containers. The samples were filtered (0.22 μ) and stored at 5°C if not immediately analysed. To 100 ml of urine sample were added 5 N KOH (10 ml) and diethyl ether (40 ml) with shaking in a separatory funnel. The upper ethereal layer was filtered, dried over anhydrous sodium sulfate and stored at -20°C (in a freezer) until assay. The organic layer was evaporated to dryness under vacuum at 30°C and the residue was subjected to GC-MS. The tea samples were processed in the same way.

2.3. Neuropsychological tests

Acute psychological and physiological effects of Hoasca tea were assessed in human subjects.

Experienced test volunteers refer to cult-members, who consume the tea anyway as members of these religious groups. Other volunteers refer to Hoasca non-users, who drink the beverage for the first time or act as controls without knowing their role. All of them were aware of the meaning of the experience, were drug-free and no concomitant disease was present. The corresponding written consent was obtained. Prior to the tea intake all the subjects were evaluated in order to assess the presence of perceptual alterations. For this purpose the Hoffer and Osmond Test (HOD test) (Ciprian-Ollivier et al., 1988) was taken, and they were neuropsychologically evaluated, to check the memory processes and visuospatial coordination. These tests were also taken 1 h after drinking the tea. The tests used were: Wais-R digit symbol test (DSY), complex-figure (Ray-Osterrieth) and the Buschke selective reminding task.

2.4. Biochemical evaluation of the Hoasca intake

Blood samples were obtained to assess cortisol, prolactin and serotonin (5-HT) levels, at hours 0:00, 1:00 and 2:00 from taking the tea. Urine samples were obtained at the same times in order to detect DMT presence.

For serum samples, the subjects need not have being fasting. Blood was collected by venipuncture into plain tubes, and allowed to clot at room temperature. After centrifugation, the serum fraction was separated, and stored. For the prolactin assays the serum samples were stable for up to 24 h at 2–8°C and frozen at -20°C for up to 1 month, while for cortisol they were under refrigeration for 7 days, or kept for up to 2 months at -20°C. Prior to these assays, the samples were allowed to come to room temperature, without thawing the frozen specimen by heating them in a water bath. For longer storage, if necessary, aliquots were prepared in order to avoid repeated freezing and thawing, and stored frozen. In our tests fresh-prepared serum samples were used when possible. To prevent interference in both the prolactin and cortisol measurements, the subjects were controlled so as not to receive any radiopharmaceuticals for diagnostic or therapeutic purposes.

2.4.1. Serotonin

Quantitation of serotonin was performed by HPLC in the serum samples of the test volunteers (normal range 45–200 ng/ml). The detailed procedure has been extensively described in previous papers (Pomilio, 1995; Vitale et al., 1995). A LKB chromatograph equipped with a LKB Bromma 2249 solvent-delivery pump, a Rheodyne injector and a fluorometric detector Chrompack (18 nm slit width, 1.5 s time constant) coupled to a LKB Bromma 2221 integrator (μBondapak C_{18}, 10 μm, 250 mm length $\times$ 4.6 mm, i.d. column); 10 μl volume injected.

2.4.2. Prolactin

Prolactin was measured in human serum by immunoradiometric assay-magnetic solid phase (normal range: 2–15 ng/ml for males and 2–26 ng/ml for premenstrual females). The Prolactin

MAIA clone kit (Serono Diagnostics, USA) was used over the range 5.0–10000 μlU/ml without dilution (detection limit: 6.0 μlU/ml). This technology incorporates two high affinity monoclonal antibodies into an immunoradiometric assay (IRMA) system to increase sensitivity and specificity compared with traditional methods (Rattle et al., 1984). Samples, standards and controls were reacted with a mixture of monoclonal antibodies to prolactin. The MAIA clone technique was used not only because of its specificity and rapid response, but also because it has the advantage that it inhibits interference in the usual IRMA techniques, such as endogenous factors causing falsely elevated values. Only grossly lipemic samples had to be discarded.

For each assay, a group of tubes was prepared in duplicate: total counts, Bo (20 μl; zero standard; absence of antigen), standards (20 μl each) of different concentrations (40, 100, 200, 500, 2000, 5000 and 10000 μU/ml), serum (20 μl) and control (20 μl). [^{125}I]-prolactin reagent (40 μl) was added to each tube, and all the tubes were gently vortexed and sealed. All the tubes except those of the total counts, were incubated for 1 h at room temp. Thoroughly mixed prolactin MAIA clone separation reagent (80 μl) was pipetted into each tube (Bo, standards, samples and controls) and all the tubes were gently vortexed. After incubation for 5 min at room temp, the rack of tubes was subjected to magnetic sedimentation for 2 min and the supernatants were carefully decanted from all the tubes. Then, diluted wash buffer (200 μl) was added to each tube. After vortex-mixing each tube, and 2 min of magnetic sedimentation, the supernatants were carefully decanted from all the tubes, drained for 5 min and blot the tubes. Each tube was counted for 60 s in a counter calibrated to detect ^{125}I. A calibration curve was run for each assay. The mean cpm was calculated for each pair of tubes and the mean cpm of the zero standard tubes was subtracted from all counts to obtain the corrected cpm.

2.4.3. Determination of cortisol

Cortisol was measured in serum samples by a ^{125}I radioimmunoassay double antibody (Diagnostic Products Corporation, USA) (normal range: 5–25 μg/dl) adequately designed for the in vitro assessment of adrenal status. This procedure is a competitive radioimmunoassay in which ^{125}I-labelled cortisol competes with the cortisol in the subject sample for antibody sites. After incubation, separation of bound from free is achieved by the PEG-accelerated double-antibody method. Finally, the antibody-bound fraction is precipitated and counted. The subject sample concentrations are read from a calibration curve as in conventional RIA techniques.

This test was selected due to the fact that the antiserum is highly specific to cortisol, with very low crossreactivity to other compounds (e.g. naturally occurring steroids or therapeutic drugs) that might be present in human samples. However, volunteers undergoing therapy with prednisolone were discarded due to the 37% observed crossreactivity with prednisolone and/or prednisone (prednisone is converted to prednisolone in vivo). Neither protein, lipemia, bilirubin (severe icterus), nor hemolysis have any effect on the assay. Only EDTA should be avoided as anticoagulant because it causes significant deviations of the measured cortisol level from that determined when serum is used. The accuracy of the assay has been further verified in patient comparison studies against two commercially available cortisol radioimmunoassays.

All components were at room temp prior to use. The tubes were labeled in duplicate: T (total counts), NSB (nonspecific binding; 10 μl of zero standard A), A (zero standard; maximum binding; 10 μl), and B through F (human serum standards containing values of cortisol 1, 5, 10, 20 and 50 μg/dl, equivalent to 27.6, 138, 276, 552 and 1380 nmol/l, respectively; 25 μl each), serum samples (25 μl each) and controls (25 μl). [^{125}I]-cortisol (40 μl) was added to the T and NSB tubes only and tubes T were counted. [^{125}I]-cortisol and cortisol antiserum (40 μl each) was added to all the tubes, except the T and NSB tubes, vortexed and incubated for 45 min at 37°C in a water bath. Thereafter the cold precipitating solution (400 μl; goat anti-rabbit γ-globulin and dilute PEG in saline) was added to all tubes, vortexed and incubated for 5 min at room tem-

perature. After centrifugation for 15 min at $3000 \times g$, the supernatants were decanted and the respective precipitates were retained for counting. Each tube was counted for 1 min. First, for each pair of tubes the average NSB-corrected cpm was calculated: net counts = average cpm − average NSB cpm. Then, the binding of each pair of tubes was determined as a percent of maximum binding (MB), with the NSB-corrected counts of the A tubes taken as 100%. The tracer has a high specific activity, with total counts of ca. 70000 cpm at iodination. Maximum binding is about 40–60%. The detection limit is about 0.3 μg/dl. Cortisol concentrations for the human volunteers were estimated by interpolation from the calibration curve.

2.5. GC-MS analysis

A 24-h urinary sample was collected without any additives, kept refrigerated during collection. The total volume (in ml) was recorded. Aliquots could be stored under refrigeration at 2–8°C for up to 7 days, or for up to 1 month frozen at −20°C. Analyses of the composition of each plant extract, liana *B. caapi* and the leaves of *P. viridis*, and the composition of Hoasca teas were performed by GC-MS. Components of the urine samples of control and test subjects (Hoasca probandi), as well as those of psychotic patients were also analysed, and matched with controls. Urine samples were taken prior to and 2 h after the administration per-os of ca. 100 ml of Ayahoasca, prepared by the members of the UDV of Brazil. A VG TRIO-2 Mass Lab apparatus with helium carrier gas was used to perform GC-MS. Split: 100:1. Column pressure: 10 psi. Data were processed by the Lab Base GC- MS data system. Mass scanning was performed in the range 30–800 for each peak sample. A SPB-1, 30 m length × 0.20 mm i.d., fused-silica capillary column was used with the following temperature programm: 60°C for 1 min, 60–290°C (10°C/min) and 5 min at 290°C. An aliquot of the organic extract, containing total alkaloids, was directly injected for GC-MS analysis.

3. Results and discussion

The results involved in this paper refer to different topics related to the knowledge of the Ayahoasca beverage or Hoasca tea, whose use is increasing worldwide especially due to its implication in religious cults. The first feature that has been considered in this paper refers to the ethnobotany and the ethnochemistry, the source-plants used and preparation and intake of the Hoasca tea context. The second is related to the chemical constituents involved, not only in the tea but also in the botanical species used to prepare it. The third refers to the neuroendocrine biochemical contribution, and the fourth is the neuropsychologic parameters. We were interested in the analysis of the short-lasting changes in perception, cognition and thought accompanying other psychological functions in consumers of Hoasca tea and comparison with psychotic subjects. Neither moral nor religious criticism was involved at all.

3.1. Ethnobotany and ethnochemistry of Hoasca tea

The use of Ayahoasca or Hoasca tea in these syncretic cults resembles the recreational aboriginal use, where visions and hallucinations play a very important role, and the members obtain, after the intake, a pleasant feeling of satisfaction, freedom, and alleviation of some physical and mental problems. The outstanding difference is that in the cults the Hoasca intake has a sacramental connotation immersed in a religious context of ethical behaviour, fraternity and respect towards other people as expected from a religion. Consequently, the Ayahoasca practice for religious purposes is allowed by the Brazilian Government owing to the psychological, social and moral profits obtained from cult-membership. Furthermore, the members belong to the middle-class and usually are politicians, executives and outstanding professionals, particularly physicians, who consume it regularly as a sacrament at certain times during the cult services, in the group ('nucleo') to which they belong, under the supervision of a 'mestre' (leader, like a priest), who has learned during months or years the corresponding

intellectual, religious and hallucinogenic-plant knowledge. Some cult-members have consumed Hoasca for over 30 years without apparent adverse health effects. On the contrary, some of them report cures of physical and mental diseases. This Ayahoasca cult-drink is usually prepared from *B. caapi* and *Psychotria* species as the only admixture, particularly the leaves of *P. viridis* or related species (*P. carthagenensis* or *P. leiocarpa*). The most common is *P. viridis*, which seems to produce more intense hallucinations than *P. carthagenensis*, while *P. leiocarpa* is similar to the first in its effects (Aranha et al., 1991). The UDV recognizes two growth forms ('tutunaka' and 'kaupuri') of *B. caapi* ('mariri'), each giving apparently different kinds of Hoasca tea. Likewise, different species of *Psychotria* used as admixtures result in a different effect of this drink.

The Ayahoasca beverage is usually prepared by the cult-people (mestre or acolysts) of each group, similar to the Ayahuasqueros. According to our results, the composition of the tea varied little from one to another close-related group, although relative differences were quoted. Preparation consists of packing layers of vine *B. caapi* alternately with leaves of *Psychotria* sp. in a vessel, water is added and the mixture is boiled in a similar way to previous detailed reports of Rivier and Lindgren (1972). When cold, the decoction is ready for consumption. There are long-time and short-time preparations of the decoctions, the former with addition of fresh water kept boiling. Some people in Brazil, not belonging to the groups that we contacted, used to swallow Ayahoasca (Lewis and Elvin-Lewis, 1977) kept in bottles as previously reported (see Section 2), and also in vessels similar to those used in Paraguay, Argentina and Uruguay for drinking the 'mate' infusion prepared with the non-hallucinogenic plant (called 'yerba mate', *Ilex paraguayensis*).

The members meet in cult-services, where Hoasca tea is drunk, the amount differing according to its concentration is controlled by the mestres, usually ca. 100–150 ml. Some of them spit and vomit, which is considered a soul purification, and immediately thereafter the visions begin. The mestre guides the visions and helps the beginners in order not to have a bad experience. The cult-members go to their work the following day, showing normal behaviour without visible signs of hallucinogen consumption. Apparently no addiction is detected. This practice resembles to a certain extent that reported previously in the Acre territory of Brazil (Prance, 1970; Prance and Prance, 1970), except for the whole religious context. Ayahoasca results in a well-controlled hallucinogenic state when compared with parenteral DMT.

Subject descriptions of the effects of Ayahoasca is related to the vision of unknown places, contact with absent or dead people, animals, valuable objects, and usually traditional or new personal aspirations. But the main characteristic is the creation of great suggestibility. Personal experiences have been previously reported in detail (Schultes, 1968; Rivier and Lindgren, 1972). The effects of the Hoasca teas that we have analysed appeared at least ca. 40 min after intake, sometimes later, and lasted for about 2 h, depending on the dose and on the individual variations, it sometimes being prolonged by taking more tea every hour. Likewise, neuroendocrine parameters suffered variations too (vide infra). Shortly after intake vegetative symptoms appear, such as tingling sensation, trembling, nausea, sometimes mydriasis, elevation of the blood pressure and an increase in the pulse rate, which disappear with the first visions. Optical illusions, pseudohallucinations and later real hallucinations, appear. At first a shining coloured veil appeared between the subject and their surroundings, and thereafter, the vision of coloured objects, geometrical visions, accompanied by a feeling of harmony and a desire to laugh and communicate with the other members. After the symptoms disappeared, they were able to describe what had happened. The visions and sensations diminished but the harmony and the spiritual lucidity remained. Furthermore, the contact with the other Hoasca drinkers appeared to remain even the day after. A light pleasant fatigue followed and there were no side-effects. These personal experiences closely resemble those reported by Rivier and the anthropologist Rüf when living with the Culina Peruvian Amazon Indians (Rivier and Lindgren, 1972; Rüf, 1972).

All cases tested in this paper reported similar good experiences, without bad sensations and/or feelings of anguish such as those caused by the hallucinogenic drink (shuri fisopa tukondi, black Ayahuasca) prepared with *B. caapi*, *P. viridis* and leaves of *Lygodium venustum* Sw. (Schizaeceae) of the Sharanahua Peruvian Amazon Indians (Rivier and Lindgren, 1972), or reported by Rodríguez and West with the yajé potion without visions, used by the witch tribe-man for medicinal purposes (Rodríguez et al., 1982).

3.2. Chemical composition of the plant material and the Hoasca teas

The plant material used for the preparation of each Hoasca tea, which we received from Brazil, was identified by the botanists, who always reported that the liane samples were those of *B. caapi*, and the leaves corresponded to *P. viridis*. Knowing that cultivars of *B. caapi* have been reported (Rivier and Lindgren, 1972; McKenna et al., 1984; Hegnauer, 1990) as well as different species of *Psychotria* and kinds of *P. viridis*, and that Hoasca may be prepared from different 'kinds' of *B. caapi* and *Psychotria* species, we especially insisted in this matter, however the botanists found no significant morphological differences in the samples. Only the alkaloids were studied in the plant materials and the drinks.

Concerning the Hoasca teas, all samples studied in this paper showed that different batches from the same cult-group were generally similar, while a variation particularly in the relative composition of the harmane alkaloids was observed from different cult-groups. Consequently, we present here the two types of Hoasca that we detected, indicating the average alkaloid composition.

Hoasca tea type 1 contained, on average, 0.065% w/v total alkaloids, t_R 15.72 min DMT (14.1%, 9.1 mg/100 ml), 19.70 min THH (6.5%, 4.2 mg/100 ml), 19.83 min *N*-Me-THH (6.3%, 4.1 mg/100 ml), 20.23 min harmaline (traces, $< 0.1\%$) and 20.47 min harmine (73.1%, 47.5 mg/100 ml) (t_R refer to GC-MS). An example of tea type 1 is shown in Fig. 1. The other typical Hoasca tea type 2, on average contained, 0.070% w/v total alkaloids, t_R 15.73 min DMT (12.5%, 8.8 mg/100 ml), 19.65 min THH (37.8%, 26.5 mg/100 ml), 19.80 min *N*-Me-THH (36.4%, 25.5 mg/100 ml), and 20.58 min harmine (13.2.1%, 9.2 mg/100 ml). An example of tea type 2 is shown in Fig. 1 Both types are different from previous *Ayahuasca* compositions reported (Rivier and Lindgren, 1972; McKenna et al., 1984). Although both types seem to be quite different several chemical properties are common, such as: the relationship of harmane alkaloids to DMT (6.5:1 and 7:1, respectively), the concentration of DMT (8.5–9.5 mg/100 ml; ca. 0.5 mM), and the total alkaloids (65–70 mg/100 ml) are all practically the same in both tea types, and furthermore, harmaline is not present or only detected in trace amounts in both cases. The main difference is the relative composition of the harmane alkaloids, THH:*N*-Me-THH:harmine being ca. 1:1:12 in type 1 tea and 3:3:1 in type 2. The differences could be related to different *B. caapi* cultivars employed to prepare the drinks, or to the method of preparation. In fact, the variable alkaloid composition in leaves and stems of *B. caapi* may be due to the presence of alkaloid-chemodems (Hegnauer, 1990), e.g. local chemical populations. Environmental variations (soil, exposure to sunlight and so on) can not be discarded. However, in this study the relative compositions of the alkaloids identified in the plants received from Brazil used for the preparation of the drinks differed from those of the drinks. The leaves of *P. viridis* contained on average 0.19–0.35% total alkaloids relative to dry weight, DMT (t_R 15.77 min) being the main component in all cases, along with traces of DMT *N*-oxide (t_R 16.57 min) and MTHC (t_R 17.30 min). No MMT was found in any of the samples of *P. viridis*. Fig. 1 is shown as an example of the leaves of *P. viridis*. In average, the stems of *B. caapi* contained 0.18% total alkaloids relative to dry wt, of which 97% was harmine (t_R 20.50 min) and 1% was THH (t_R 19.70 min). Some stems contained only harmine and traces or none of THH. Neither harmaline, harmol nor methoxytryptamines were detected in the samples of *B. caapi* (Fig. 1).

The GC-MS were analysed, and the mass fragmentograms of the alkaloidal extracts of *B. caapi* samples, *P. viridis* samples and beverages were monitored for the occurrence of traces of the

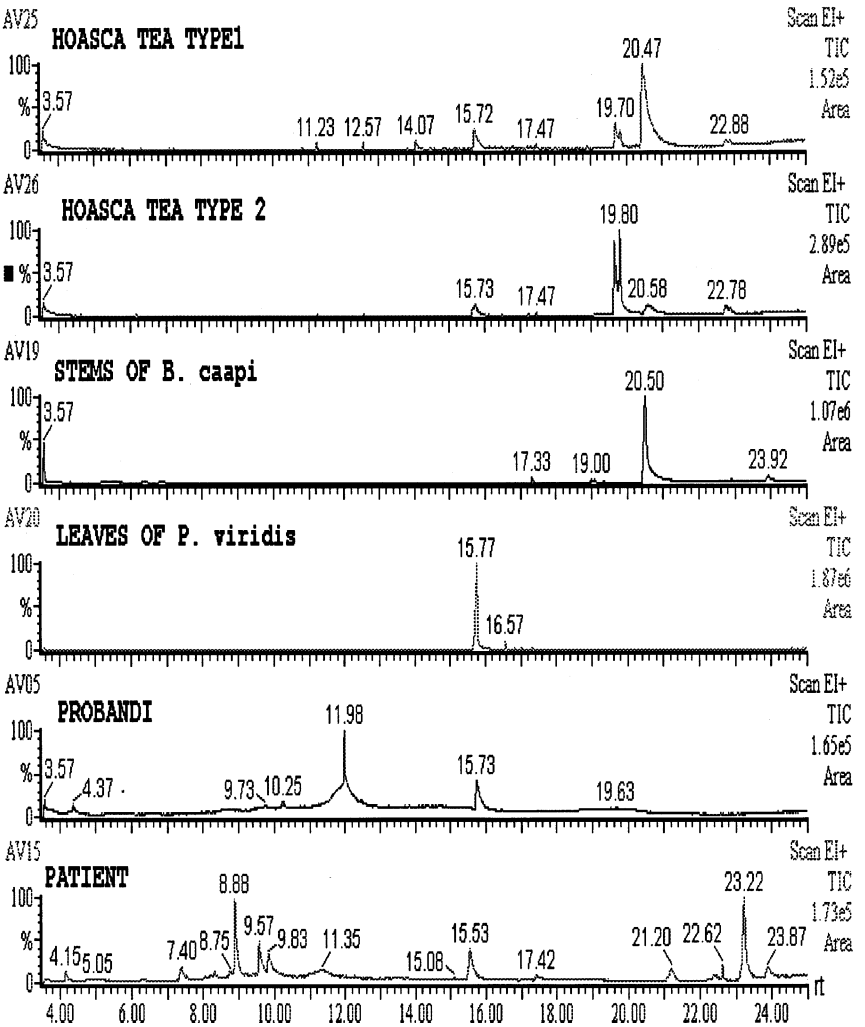

Fig. 1. Examples of GC-MS of Hoasca tea, leaves of *P. viridis*, stems of *B. caapi*, Probandi and patients.

known indoleamines and β-carbolines focussing on the respective mass numbers of the base peaks and molecular ions. The mass fragmentation was in agreement with previous reports (Holmstedt and Lindgren, 1967; Rivier and Lindgren, 1972). Concerning tryptamines, in these samples only DMT was obtained, along with its *N*-oxide. DMT: 30, 42, 58 (bp), 77, 103, 130, 188 (M) (Holmstedt and Lindgren, 1967). DMT *N*-oxide: 58 (bp), 103, 115, 130, 143, 188, 204 (M). MTHC (2-methyl-1,2,3,4-tetrahydro-β-carboline): 78, 102, 115, 143 (bp), 186 (M) (Agurell et al., 1969; Rivier and Lindgren, 1972). Harmine (1-methyl-7-methoxy-β-carboline): 44, 63, 75, 106, 169, 212 (bp and M) (Holmstedt and Lindgren, 1967). Harmaline (1-methyl-7-methoxy-3,4-dihydro-β-carboline): 169, 170, 186, 198, 199, 212, 213, 214 (bp and M) (Rivier and Lindgren, 1972). THH (1-methyl-7-methoxy-1,2,3,4-tetrahydro-β-carboline): 43, 44, 57, 91, 158, 172, 201 (bp), 216 (M) (Holmstedt and Lindgren, 1967). *N*-Me-THH (1,2-dimethyl-7-methoxy-1,2,3,4-tetrahydro-β-carboline): 43, 44, 57, 85, 172, 201, 215 (bp), 230 (M).

The β-carbolines and DMT concentrations present in the two types of Hoasca teas are differ-

ent from those previously reported from the Peruvian Amazon (Rivier and Lindgren, 1972; McKenna et al., 1984) and are nearly intermediate. However, in the case of these hallucinogenic drinks what is important is the relative concentration of harmane alkaloids and DMT, and the corresponding harmane levels to cause MAO inhibition. The amounts of β-carbolines in the typical dose of these two types of Hoasca teas are well below the threshold at which they are hallucinogens themselves (ca. 300–500 mg for harmaline and THH; ca. 1000 mg for harmine, and 400 mg for physical symptoms (Pennes and Hoch, 1957; Naranjo, 1967)), but well within the range for acting as highly selective inhibitors of MAO-A, the form for which serotonin, and other tryptamines (e.g. DMT) are the preferred substrates (Yasuhara et al., 1972). In vitro, β-carbolines are MAO inhibitors at ca. 10 mM (Buckholtz and Boggan, 1977; McKenna et al., 1984) which is 2 to 3 orders of magnitude lower than the hallucinogenically active dose. Nevertheless, greater amounts of β-carbolines than those detected here would be necessary for their hallucinogenic effect, owing to the non-synergistic β-carbolines mechanism (McKenna et al., 1984). In spite of the low DMT levels obtained here they are still well within its activity range, which is lower than i.m. (Szára, 1956) or i.v. (Strassman, 1994; Strassman and Qualls, 1994; Strassman et al., 1994) DMT threshold under conditions of MAO inhibition.

This selectivity of β-carbolines for MAO-A over MAO-B, combined with their relatively low affinity for liver MAO compared to brain MAO, may explain why there are no risk of hypertensive crises post-ingestion of Ayahuasca, particularly in subjects who consume tyramine-containing foods (Yasuhara et al., 1972). Urine samples were analysed by GC-MS (Vitale et al., 1995), showing four groups according to DMT response. First, all controls were free from DMT. Second, all subjects (new and common users) showed the presence of DMT in the urine post Ayahoasca, which was possitively correlated with the perceptual alterations. Third, prior to the tea intake, DMT was detected only in the urine samples of usual consumers of Ayahoasca. Finally, urine samples from drug-free acute schizophrenic patients showed DMT occurrence. A GC-MS example of a positive-DMT subject urine after Hoasca intake is given in Fig. 1 (t_R 10.25 min: caffeine; 11.98 min urea; 15.73 min DMT). Further, an example of the urine analysis of an acute schizophrenic patient, who had not taken Hoasca tea is also given in Fig. 1 (t_R 15.53 min DMT; 17.42 min acridine derivative; 21.20 min sitosterol; 23.22 min cholesterol; 23.87 min stigmasta-3,5-dien-7-one; the three latter peaks probably from dietary origin).

3.3. Neuroendocrine measurements

Blood samples were assayed for serotonin, prolactin and cortisol prior to and after ingestion of Hoasca in order to obtain information about the serotonergic response to Hoasca.

As is known, cortisol is the major glucocorticoid secreted by the adrenal cortex, and is physiologically effective in anti-inflamatory and blood pressure maintenance, and is also involved in gluconeogenesis, calcium adsorption and the secretion of gastric acid and pepsin. Measurement of blood cortisol levels is especially useful as an indicator of adrenocortical function. Circulating cortisol is usually determined using stimulation and suppression tests, such as ACTH stimulation, ACTH reserve (metyrapone suppression) and dexamethasone suppression, which provide supportive information on adrenocortical function. However, anomalous cortisol concentrations were obtained in patients with acute infection, severe pain, diabetes mellitus, heart failure and in women, either pregnant or on estrogen therapy, as well as in certain virilizing syndromes and iatrogenic conditions which raise other natural steroids to unphysiologic high concentrations. Therefore, in this study we used the highly specific double antibody radioimmunoassay (detection limit about 0.3 μg/dl) to prevent the interferences observed with less specific antisera used in other RIA procedures (Diagnostic Products Corporation, 1985).

Human prolactin is a hormone secreted by the anterior pituitary gland under the direct control of the hypothalamus, the thyrotrophin releasing hormone (TRH) being known to have a stimula-

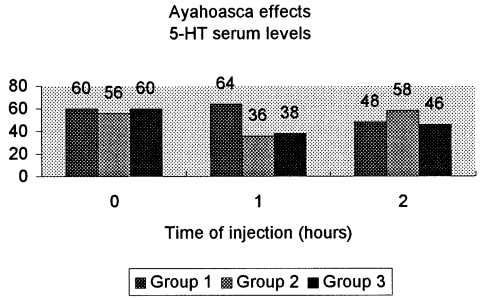

Fig. 2. Ayahoasca effects: 5-HT serum levels.

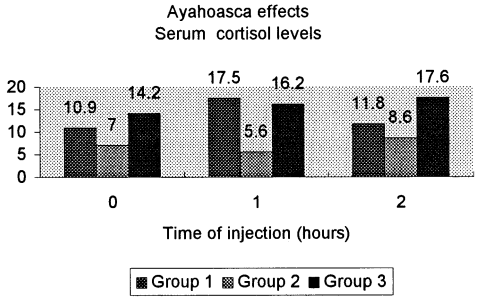

Fig. 4. Ayahoasca effects: serum cortisol levels.

tory effect upon prolactin secretion. A lot of known physiological states are associated with hyperprolactinemia, therefore, we performed the measurement of prolactin in serum as an index of functional disorder within the hypothalamic pituitary axis.

Results of serotonin, prolactin and cortisol levels are shown in Figs. 2–4, respectively.

Sequential measures of prolactin and cortisol showed significant responses in blood levels nearly 1 h after Ayahoasca intake in agreement with the beginning of the hallucinogenic effect, and the subjects could be grouped accordingly. One group of Hoasca new consumers showed increasing neuroendocrine response, which correlated with a pronounced perceptual response, and in agreement with previous dose-dependent studies with synthetic DMT and other hallucinogens (Prescott et al., 1984; Tuomisto and Mannisto, 1985; Van der Karr et al., 1989; Strassman, 1994; Strassman and Qualls, 1994; Strassman et al., 1994), such as lysergic acid diethylamide (LSD), which have been shown to act mainly via serotonin 5-HT2 receptors, although the exact mechanism of their action is still unknown. Pupil diameter, mean arterial blood pressure, pulse, and core temperature also rose dose-dependently.

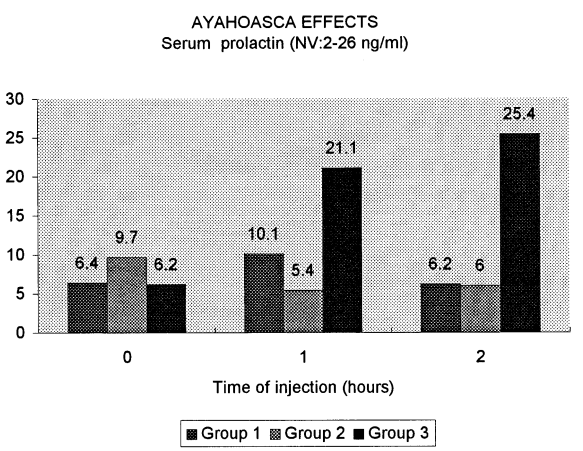

Fig. 3. Ayahoasca effects: serum prolactin levels.

Neuroendocrine blood levels and heart rate responses demonstrated significant reductions across administrations, suggesting tolerance (second grouping), similar to DMT administration. Although the lack of psychological tolerance supported a role for DMT in natural-occurring psychoses (Strassman, 1994; Strassman et al., 1994).

The third group showed, instead, a continued rise in both cortisol and prolactin, along with a decrease in serotonin. In all cases the response was short in time, but could be maintained with a second intake 1 h after the first drink. The three groups evidenced expected different perceptual effects with values in agreement with the individual biochemical responses, indicating that psychedelic effects may be required to perturb biological effects. All these effects may be mediated by 5-HT-2A, 5-HT-2C, or 5-HT-1A subtype activation, as in the case of DMT (Strassman, 1994; Strassman et al., 1994).

The determination of the receptor subtype accounting for the effects of psychedelic compounds is hampered by the fact that 5-HT-2 receptors belong to a family of pharmacologically and structurally closely related receptors: 5-HT2, 5-HT1C and the recently cloned 5-HT2F. It has been proposed to re-name these receptors as 5-HT2A, 5-HT2C and 5-HT2B, respectively. In

contrast with the rat brain, in the human brain it has not been possible until now to visualize the mRNA's coding for the 5-HT2A and the 5-HT2C receptors. The pharmacological characteristics of 5-HT2A and 5-HT2C receptors differ among species, and there are also differences in 5-HT2C receptors distribution in the human brain as compared to the rat brain. The human anatomical studies on the distribution of serotonin receptors suggest that the possible targets for the action of hallucinogenic drugs is widespread, and could be associated with neocortical, limbic and also with mechanisms mediated through the basal ganglia in the human brain (Palacios et al., 1994).

3.4. Neuropsychological parameters

Results from the HOD test and neuropsychological evaluation are shown in Figs. 5 and 6.

Once the beverage was taken by the subjects, no effects were reported up to 35 min after intake, at this moment one group of subjects reported marked perceptual alterations in the sense of distortion of true perceptions, mainly visual. No auditory hallucinations were reported at any time by the subjects. Meanwhile two groups of subjects experienced strong perceptual alterations, as shown in Fig. 5, the other only reported slight time–space disorientation. All of them experienced changes in mood, with unmotivated laughing. The effect on neuropsychological tasks was

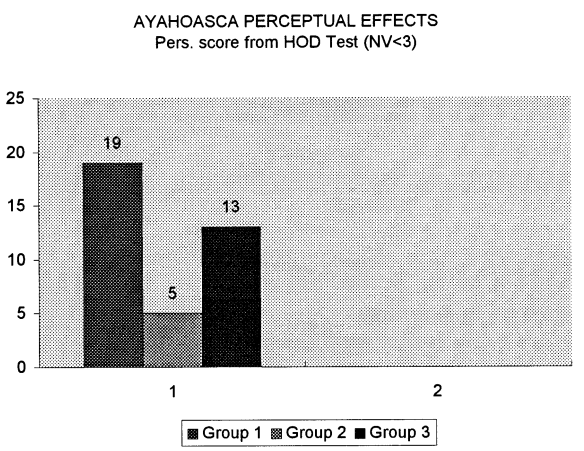

Fig. 5. Ayahoasca perceptual effects.

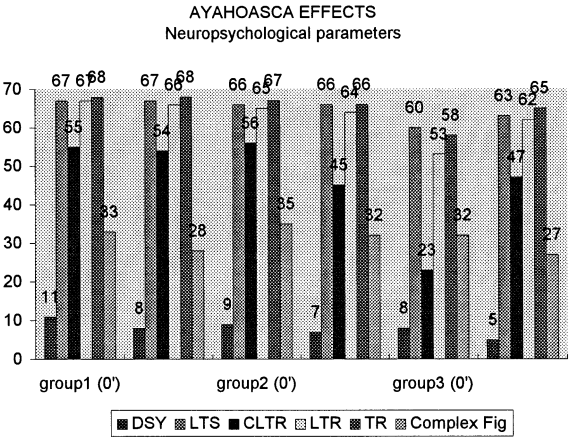

Fig. 6. Ayahoasca effects: neuropsychological parameters.

significative (Fig. 6). The comparison of the results shows that Ayahoasca had slight effects on attention and memory processes and stronger effects on visuospatial construction. The Wais-R digit symbol test (DSY) decreased significatively after the tea, meaning interference with sustained attention. The Buschke selective reminding task showed a decrease in consistent long term retrieval (CLTR) but not significative changes in long term storage (LTS), long term retrieval (LTR) and total recall (TR). Visuoperceptual processes were significatively affected, as shown by the results of the complex-figure (Ray-Osterrieth).

The perceptual distortions are primarily visual in nature, light flashes, colours, abstract forms and figures, illusions, primarily geometrical patterns, moving very fast, having sometimes very deep emotional content and connotation. There is an inability to keep attention focused on any outside event. There is an enhanced dependence on the environment for structure and for symbolic meanings, and increased association. It is outstanding the rapid onset and the short-lasting effect.

4. Conclusions

GC-MS analysis of samples of Ayahoasca beverage and plant material, showed the presence of β-carbolines and DMT, leading mainly to two

types of tea according to the quantitative results. Moreover, urine samples of psychotic unmedicated patients also gave DMT resembling those of the Ayahoasca new and usual consumers. In Ayahoasca β-carbolines as strong MAO inhibitors prevent DMT from being destroyed by liver MAO in the first pass effect. Therefore, DMT reaches and crosses the BBB, exerting 5-HT2 agonist effects on the CNS. This 5-HT2 agonism accounts for the biological and behavioural disturbances induced by the tea (Eison, 1994). The biochemical profile of volunteers under the effects of Ayahoasca was studied. Neuroendocrine and neuropsychological data before and after Hoasca intake were determined to assess differences between Hoasca drinkers and controls.

Decreased MAO kinetics have been previously reported in schizophrenia by several authors (Davis et al., 1982). It is assumed that this phenomenon may be the basis for the non destruction and consequent accumulation of methylated indolealkylamines, such as DMT, in these patients. Our previous papers on the subject were always related to the occurrence of this compound in urine from psychiatric patients and the level of perceptual alterations (Ciprian-Ollivier et al., 1986; Ciprian-Ollivier, 1991). This is also shown in this report on Ayahoasca owing to the strong effects on perception (see neuropsychological results).

Furthermore, the neuropsychological findings support that Ayahoasca affects more visuospatial functions, due to subtle perceptual interference, than cognitive processes. In this study this was confirmed by the HOD test results, which clearly recorded perceptual alterations in all three groups of subjects.

Biological parameters led us to think about a serotonergic agonism, mainly over 5-HT2 receptors. These receptors have been involved in a regulatory effect on synthesis and release of DA, and also explain the rise in prolactin levels (Heym and Jacobs, 1987; Iqbal et al., 1991; Lindenmayer, 1992). Serotonin has also a regulatory effect on hypothalamic cortisol regulation, in a way that 5-HT2 receptors agonism can raise cortisol levels. Both, at least, in first-time consumers.

Recently, and especially in the last few years, interest was focused on serotonergic mechanisms in psychoses pathogenesis in relation to the mechanism of action of the so called 'atypical antipsychotics' (Müller-Spahn, 1992; Wong et al., 1994). However, the 'transmethylation hypothesis of schizophrenia' proposed this participation more than 35 years ago (Wyatt and Gillin, 1976) but received little attention. Thus, clozapine, risperidone, ritanserine (Davis et al., 1991) show a mechanism of action, which also involves the ability to interact with several 5-HT receptors (Nelson et al., 1994; Kuccharewicz et al., 1994; Strassman, 1994; Strassman and Qualls, 1994; Strassman et al., 1994), the most important being 5-HT2. Actually, DMT interacts with this receptor. We can hypothesize that part of the antipsychotic effect may be related to blocking DMT activity on this receptor by the new antipsychotics (Aghajanian and Marek, 1994; Ciccocioppo et al., 1994; Costall and Naylor, 1994; Donetti et al., 1994; Johnson et al., 1994).

On the other hand, strong relationships between 5-HT and DA neuron activity was reported (Steward et al., 1994). In summary, this in vivo study represents an additional step towards understanding the psychopharmacology of Ayahoasca and further confirms that Ayahoasca represents an experimental psychosis with common features with the transmethylation hypothesis of schizophrenia, encouraging further research.

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