# 10. The Scientific Investigation of Ayahuasca: A Review of Past and Current Research

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## Introduction

Of the numerous plant hallucinogens utilized by indigenous populations of the Amazon Basin, perhaps none is as interesting or complex, botanically, chemically, or ethnographically, as the hallucinogenic beverage known variously as *ayahuasca* , *caapi*, or *yage*. The beverage is most widely known as *ayahuasca*, a Quechua term meaning "vine of the souls," which is applied both to the beverage itself and to one of the source-plants used in its preparation, the Malpighiaceous jungle liana, *Banisteriopsis caapi* (Schultes, 1957). In Brazil, transliteration of this Quechua word into Portuguese results in the name, *Hoasca. Hoasca*, or *ayahuasca*, occupies a central position in Mestizo ethnomedicine, and the chemical nature of its active constituents and the manner of its use makes its study relevant to contemporary issues in neuropharmacology, neurophysiology, and psychiatry.

## Traditional and Indigenous Uses of Ayahuasca

The use of *ayahuasca* under a variety of names is a widespread practice among various indigenous aboriginal tribes endemic to the Amazon Basin (Schultes, 1957). Such practices undoubtedly were well established in pre-Columbian times, and in fact may have been known to the earliest human inhabitants of the region. Iconographic depictions on ceramics and other artifacts from Ecuador have provided evidence that the practice dates to at least 2000 B.C. (Naranjo, 1986). Its widespread distribution among numerous Amazonian tribes also argues for its relative antiquity.

Considerable genetic intermingling and adoption of local customs followed in the wake of European contact, and *ayahuasca*, along with a virtual pharmacopoeia of other medicinal plants, gradually became integrated into the ethnomedical traditions of these mixed populations. Today the drug forms an important element of ethnomedicine and shamanism as it is practiced among indigenous Mestizo populations in Peru, Colombia, and Ecuador. The sociology and ethnography of the contemporary use of *ayahuasca* (as it is most commonly termed) in Mestizo ethnomedicine has been extensively described (Dobkin de Rios, 1972, 1973; Luna, 1984, 1986)

### Syncretic Religious Use of Ayahuasca

From the perspective of the sociologist or the ethnographer, discussion of the use of *ayahuasca* or *ayahuasca* can conveniently be divided into a consideration of its use among indigenous aboriginal and mestizo populations, and its more recent adoption by contemporary syncretic religious movements such as the União do Vegetal (UDV), Barquena, and Santo Daime sects in Brazil. It is within the context of acculturated groups such as these that questions regarding the psychological, medical, and legal aspects of the use of *ayahuasca* become most relevant, and also, most accessible to study.

The use of *ayahuasca* in the context of mestizo folk medicine closely resembles the shamanic uses of the drug as practiced among aboriginal peoples. In both instances, the brew is used for curing, for divination, as a diagnostic tool and a magical pipeline to the supernatural realm. This traditional mode of use contrasts from the contemporary use of *ayahuasca* tea within the context of Brazilian syncretic religious movements. Within these cults, the members consume *ayahuasca* tea at regular intervals in group rituals in a manner that more closely resembles the Christian Eucharist than the traditional aboriginal use. The individual groups of the UDV, termed *nucleos*, are similar to a Christian Hutterite sect, in that each group has a limited membership, which then splits to form a new group once the membership expands beyond the set limit. The *nucleo* consists of the congregation, a group leader or mestre, various acolytes undergoing a course of study and training in order to become mestres, and a temple, an actual physical structure where the sacrament is prepared and consumed at prescribed times, usually the first and third Saturday of each month. The membership of these newer syncretic groups spans a broad socio-economic range and includes many educated, middle-class, urban professionals (including a number of physicians and other health professionals). Some older members have engaged in the practice for 30 or more years without apparent adverse health effects. The UDV and the Santo Daime sects are the largest and most visible of several syncretic religious movements in Brazil that have incorporated the use of *ayahuasca* into their ritual practices. Of the two larger sects, it is the UDV that possesses the strongest organizational structure as well as the most highly disciplined membership. Of all the *ayahuasca* churches in Brazil, the UDV has also been the most pivotal in convincing the government to remove *ayahuasca* from its list of banned drugs. In 1987, the government of Brazil approved the ritual use of

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*hoasca* tea in the context of group religious ceremonies. This ruling has potentially significant implications, not only for Brazil, but for global drug policy, as it marks the first time in over 1600 years that a government has granted permission to its non-indigenous citizens to use a psychedelic in the context of religious practices.

## Botanical, Chemical, and Pharmacological Aspects of *Ayahuasca*

*Ayahuasca* is unique in that its pharmacological activity is dependent on a synergistic interaction between the active alkaloids in the plants. One of the components, the bark of *Banisteriopsis caapi*, contains ß-carboline alkaloids, which are potent MAO-A inhibitors; the other component, the leaves of *Psychotria viridis* or related species, contains the potent short-acting psychoactive agent N,N-dimethyltryptamine (DMT). DMT is not orally active when ingested by itself, but can be rendered orally active in the presence of a peripheral MAO inhibitor - and this interaction is the basis of the psychotropic action of *ayahuasca* tea (McKenna, Towers, & Abbott, 1984).

### *1. Botanical sources of ayahuasca*

In a traditional context, *Ayahuasca* is a beverage prepared by boiling - or soaking - the bark and stems of *Banisteriopsis caapi* together with various admixture plants. The admixture employed most commonly is the Rubiaceous genus *Psychotria*, (Rubiaceae), particularly *P. viridis*. The leaves of *P. viridis* contains alkaloids which are necessary for the psychoactive effect (see the sections on chemistry and pharmacology, below). There are also reports (Schultes, 1972) that other *Psychotria* species, *especially P. leiocarpa* or *P. carthaginensis*, are used instead of *P. viridis*, but such reports may be due to a botanical misidentification; in any case, use of *Psychotria* species other *than P. viridis* is rare. In the Northwest Amazon, particularly in the Colombian Putumayo and Ecuador, the leaves of *Diplopterys cabrerana*, a jungle liana in the same family as *Banisteriopsis*, are added to the brew in lieu of the leaves of *Psychotria.* The alkaloid present in *Diplopterys*, however, is identical to that in the *Psychotria* admixtures, and pharmacologically, the effect is the same. In Peru, various admixtures in addition to *Psychotria* or *Dipolopterys* are frequently added, depending on the magical, medical, or religious purposes for which the drug is being consumed. Although a virtual pharmacopoeia of admixtures are occasionally added, the most commonly employed admixtures (other than *Psychotria*, which is a constant component of the preparation) are various Solanaceous genera, including tobacco (*Nicotiana* sp.), *Brugmansia* sp., and *Brunfelsia* sp. (Schultes, 1972; McKenna, et al., 1995). These Solanaceous genera are known to contain alkaloids, such as nicotine, scopalamine, and atropine, which effect both central and peripheral adrenergic and cholinergic neurotransmission. The interactions of such agents with serotonergic agonists and MAO inhibitors are essentially unknown in modern medicine.

### *2. Chemistry of Ayahuasca and its source plants*

The chemical constituents of *ayahuasca* and the source-plants used in its preparation have been well characterized (McKenna, et al., 1984; Rivier & Lindgren, 1972). *Banisteriopsis caapi* contains the ß-carboline derivatives harmine, tetrahydroharmine, and harmaline as the major alkaloids (Callaway, et al., 1996). Trace amounts of other ß-carbolines have also been reported (McKenna, et al., 1984; Rivier & Lindgren, 1972; Hashimoto and Kawanishi, 1975, 1976) as well as the pyrrolidine alkaloids shihunine and dihydroshihunine (Kawanishi et al. 1982). The admixture plant, *Psychotria viridis*, contains a single major alkaloid, N,N-dimethyltryptamine (DMT), while N-methyl tryptamine and methyl-tetrahydro-ß-carboline have been reported as trace constituents (McKenna, et al., 1984; Rivier & Lindgren, 1972). The admixture plant *Psychotria carthagenensis* has been reported to contain the same alkaloids (Rivier & Lindgren, 1972) but a subsequent investigation could not confirm the presence of DMT in the single collection examined (McKenna, et al., 1984). The concentrations of alkaloids reported in *Banisteriopsis caapi* range from 0.05 % dry weight to 1.95 % dry weight; in *Psychotria*, the concentration of alkaloids ranged from 0.1 to 0.66 % dry weight (McKenna, et al., 1984; Rivier & Lindgren, 1972). Similar ranges and values were reported by both groups of investigators.

The concentrations of alkaloids in the *ayahuasca* beverages are, not surprisingly, several times greater than in the source plants from which they are prepared. Based on a quantitative analysis of the major alkaloids in several samples of *ayahuasca* collected on the upper Rio Purús, Rivier & Lindgren (1972) calculated that a 200 ml dose of *ayahuasca* contained an average of 30 mg of harmine, 10 mg tetrahydroharmine, and 25 mg DMT. Callaway, et al., determined the following concentrations of alkaloids in the *hoasca* tea utilized in the biomedical study with the UDV (mg/ml): DMT, 0.24; THH, 1.07; harmaline, 0.20; and harmine 1.70. A typical 100 ml dose of hoasca thus contains in mg: DMT, 24; THH, 107; harmaline, 20; harmine, 170. Interestingly, these concentrations are above the threshold of activity for i.v. administration of DMT (Strassman & Qualls, 1994).

McKenna et al. (1984) reported somewhat higher values for the alkaloid content of several samples of Peruvian ayahausca. These investigators calculated that a 100 ml dose of these preparations contained a total of 728 mg total alkaloid, of which 467 mg is harmine, 160 mg is tetrahydroharmine, 41 mg is harmaline, and 60 mg is DMT. This is well within the range of activity for DMT administered i.m. (Szara, 1956) or i.v. (Strassman & Qualls, 1994) and is also well within the range for harmine to act effectively as a monoamine oxidase inhibitor (MAOI).

In vitro, these ß-carbolines function as MAOI at approximately 10 nM (e.g., harmine's $IC_{50}$ for MAOI is ~1.25 x $10^{-8}$ M; cf. McKenna, et al., 1984; Buckholtz & Boggan, 1977). In mice, harmaline administered i.p. at 5 mg/kg causes 100% inhibition by 2 hours post-injection, the activity falling off rapidly thereafter (Udenfriend et al. 1958) This dose corresponds to approximately 375 mg in a 75 kg adult, but, based on the measured concentration of harmine in the liver, it is likely that one half this dose or less would also be effective. The reasons for the discrepancy in alkaloid concentrations between the samples examined by Rivier & Lindgren (1972) and those examined by McKenna, et al. (1984) are readily explained by the differences in the methods of preparation. The method employed in preparing *ayahuasca* in Pucallpa, Peru, where the samples analyzed by McKenna et al. (1984) were collected, results in a much more concentrated brew than the method employed on the upper Rio Purús, the region which was the source of the samples examined by Rivier & Lindgren. The concentrations and proportions of alkaloids can vary significantly in different batches of *ayahuasca,* depending on the method of preparation, as well as the amounts and proportions of the source-plants.

The notion that the ß-carbolines, by themselves, are hallucinogenic and thus contribute to the overall hallucinogenic activity of the ayahuasca beverage, was based on flawed earlier research (Naranjo, 1967) and has been discredited (Callaway, et al., 1997). As MAO inhibitors, ß-carbolines can increase brain levels of serotonin, and the primarily sedative effects of high doses of ß-carbolines are thought to result from their blockade of serotonin deamination. The primary action of ß-carbolines in the ayahuasca beverage is their inhibition of peripheral MAO-A, which protects the DMT in the brew from peripheral degradation and thus renders it orally active. There is some evidence, however, that tetrahydroharmine (THH), the second most abundant ß-carboline in the beverage, acts as a weak 5-HT uptake inhibitor and MAOI. Thus, THH may prolong the half-life of DMT by blocking its intraneuronal uptake, and hence, its inactivation by MAO, localized in mitochondria within the neuron. On the other hand, THH may block serotonin uptake into the neuron, resulting in higher levels of 5HT in the synaptic cleft; this 5-HT, in turn, may attenuate the subjective effects of orally ingested DMT by competing with it at post-synaptic receptor sites (Callaway, et al., 1997).

### *3. Pharmacological actions of Ayahuasca and its Active Alkaloids*

The hallucinogenic activity of *ayahuasca* is a function of the peripheral inactivation of MAO by the ß-carboline alkaloids in the mixture. This action prevents the peripheral oxidative deamination of the DMT, which is the primary hallucinogenic component, rendering it orally active and enabling it to reach its site of action in the CNS in an intact form. (McKenna, et al 1984; Schultes, 1972). DMT alone is inactive following oral administration at doses up to 1000 mg (Shulgin, 1982; Nichols, et al. 1991). DMT is active by itself following parenteral administration starting at around 25 mg (Szara, 1956; Strassman & Qualls, 1994). Because of its oral inactivity, various methods of parenteral administration are employed by users. For example, synthetic DMT is commonly smoked as the free base; in this form, the alkaloid volatilizes readily and produces an immediate, intense psychedelic episode of short duration (5 -15 min), usually characterized by multicolored, rapidly moving visual patterns behind the closed eyelids (Stafford, 1977). The Yanomamo Indians and other Amazonian tribes prepare a snuff from the sap of various trees in the genus *Virola*, which contain large amounts of DMT and the related compound, 5-methoxy-DMT, which is also orally inactive (McKenna, et al. 1985; Schultes and Hofmann, 1980). The effects of the botanical snuffs containing DMT, while not as intense as smoking DMT free base, are similarly rapid in onset and of limited duration [unpublished data]. The *ayahuasca* beverage is unique in that it is the only traditionally used psychedelic where the enzyme-inhibiting principles in one plant (ß-carbolines) are used to facilitate the oral activity of the psychoactive principles in another plant (DMT). The psychedelic experience that follows ingestion of *ayahuasca* differs markedly from the effects of parenterally ingested DMT; the time of onset is approximately 35-40 minutes after ingestion, and the effects, which are less intense than parenterally administered synthetic DMT, last approximately four hours. The subjective effects of *ayahuasca* include phosphene imagery seen with the eyes closed, dream-like reveries, and a feeling of alertness and stimulation. Peripheral autonomic changes in blood pressure, heart-rate, etc., are also less pronounced in *ayahuasca* than parenteral DMT. In some individuals, transient nausea and episodes of vomiting occur, while others are rarely affected in this respect. When *ayahuasca* is taken in a group setting, vomiting is considered a normal part of the experience and allowances are made to accommodate this behavior (Callaway, et al., 1997).

The amounts of ß-carbolines present in a typical dose of *ayahuasca* are well above the threshold for activity as MAOI. It is likely that the main contribution of the ß-carbolines to the acute effects of *ayahuasca* results from their action as peripheral MAO inhibitors, rendering DMT orally active. It is worthy of note that ß-carbolines are highly selective inhibitors of MAO-A, the form of the enzyme for which serotonin, and presumably other tryptamines, including DMT, are the preferred substrates (Yasuhara, et al., 1972; Yasuhara, 1974). This selectivity of ß-carbolines for MAO-A over MAO-B, combined with their relatively low affinity for liver MAO compared to brain MAO, may explain why reports of hypertensive crises following the ingestion of *ayahuasca* have not been documented. On the other hand, Suzuki et al. (1981) has reported that DMT is primarily oxidized by MAO-B; it is

possible, therefore, that high concentrations of ß-carbolines, partially inhibit MAO-B as well as MAO-A; but the greater affinity of tyramine for MAO-B enables it to compete for binding to the enzyme and displace any residual ß-carbolines. This mechanism would explain the lack of any reports of peripheral autonomic stimulation associated with the ingestion of *ayahuasca* in combination with foods containing tyramine (Callaway, et al., 1997).

DMT and its derivatives and the ß-carboline derivatives are widespread in the plant kingdom (Allen & Holmstedt, 1980) and both classes of alkaloids have been detected as endogenous metabolites in mammals, including man (Bloom, et al. 1982; Barker, et al. 1981a; Airaksinen & Kari, 1981). Methyl transferases which catalyze the synthesis of DMT, 5-methoxy-DMT, and bufotenine have been characterized in human lung, brain, blood, cerebrospinal fluid, liver, and heart, and also in rabbit lung, toad, mouse, steer, guinea pig, and baboon brains, as well as in other tissues in these species (McKenna & Towers, 1984). Although the occurrence, synthesis, and degradative metabolism of DMT in mammalian systems has been the focus of recent scientific investigations (Barker, et al. 1981b). Endogenous psychotogens have been suggested as possible etiological factors in schizophrenia and other mental disorders, but the evidence remains equivocal (Fischman, 1983). The candidacy of DMT as a possible endogenous psychotogen essentially ended when experiments showed comparable levels in both schizophrenics and normals; at present the possible neuroregulatory functions of this "psychotomimetic" compound are incompletely understood, but Callaway (1988) has presented an interesting hypothesis regarding the possible role of endogenous DMT and ß-carbolines in regulating sleep cycles and REM states.

ß-carbolines are tricyclic indole alkaloids that are closely related to tryptamines, both biosynthetically and pharmacologically. They are readily synthesized by the condensation of indoleamines with aldehydes or alpha-keto acids, and their biosynthesis probably also proceeds via similar reactions (Callaway et al., 1994). ß-carbolines have also been identified in mammalian tissue, including human plasma and platelets, and rat whole brain, forebrain, arcuate nucleus, and adrenal glands (Airaksinen and Kari, 1981). 6-methoxy-tetrahydro-ß-carboline has been recently identified as a major constituent of human pineal gland (Langer et al. 1984). This compound inhibits the high-affinity binding of [$^3$H]-imipramine to 5-HT receptors in human platelets (Langer et al. 1984), and also significantly inhibits 5-HT binding to type 1 receptors in rat brain; the compound has a low affinity to type 2 receptors, however (Taylor et al. 1984). 2-methyl-tetrahydro-ß-carboline and harman have been detected in human urine following ethanol loading, (Rommelspacher, et al., 1980) and it has been suggested that endogenous ß-carbolines and other amine-aldehyde condensation products may be related to the etiology of alcoholism (Rahwan, 1975). At least one ß-carboline has been identified as a by-product of the oxidative metabolism of DMT in rat brain homogenates (Barker, et al. 1980).

ß-carbolines exert a variety of neurophysiological and biological effects (McKenna and Towers, 1984). ß-carboline derivatives are selective, reversible, competitive inhibitors of MAO-A (Buckholtz and Boggan, 1976, 1977). Other neurophysiological actions of ß-carbolines include competitive inhibition of the uptake of 5-HT, dopamine, epinephrine, and norepinephrine into synaptosomes (Buckholtz and Boggan, 1976; Pähkla, et al., 1997)), inhibition of $Na^+$ dependent membrane ATPases (Canessa, et al. 1973), interference with biosynthesis of biogenic amines (Ho, 1977), and vasopressin-like effects on sodium and water transport in isolated toad skin (de Sousa and Gross, 1978). ß-carboline-3-carboxylate and various esterified derivatives have been implicated as possible endogenous ligands for benzodiazepine receptors (Lippke et al. 1983). ß-carboline ligands of these receptors can induce epileptiform seizures in rats and in chickens homozygous for the epileptic gene (Morin, 1984, Johnson, et al. 1984); this proconvulsant action can be blocked by other receptor ligands, including diazepam and ß-carboline-carboxylate propyl ester (Morin, 1984, Johnson, et al. 1984).

ß-carbolines also exhibit other biological activities in addition to their effects on neuro-physiological systems. For instance Hopp and co-workers found that harmine exhibited significant anti-trypanosomal activity against *Trypanosoma lewisii* (Hopp et al., 1976). This finding may explain the use of *ayahuasca* in mestizo ethnomedicine as a prophylactic against malaria and internal parasites (Rodriguez, et al. 1982). Certain ß-carbolines are known to exert mutagenic or co-mutagenic effects, and the mechanism responsible may be related to their interactions with nucleic acids (Umezawa, et al. 1978; Hayashi, et al. 1977). The ultra-violet activated photocytotoxic and photogenotoxic activity of some ß-carbolines has also been reported (McKenna & Towers 1981; Towers & Abramosky, 1983).

**Recent Biomedical Investigations of Ayahuasca**

Although achieving some notoriety in North American literature through the popular press and the writings of William Burroughs and Allan Ginsberg (Burroughs and Ginsberg, 1963), the psychological and physiological phenomena induced by *ayahuasca* have received little or no rigorous study. Various travelers to the Amazon have reported their own first hand experiences with *ayahuasca* (Weil, 1980), while both formal and informal ethnographic narratives have excited the public imagination (Lamb, 1971; Luna and Amaringo, 1991). Interest in the exotic origins and effects of ayahuasca have attracted a steady stream of North American tourists, often enticed by articles and advertisements in popular and New Age magazines (Krajick, 1992; Ott, 1993). Concern over possible adverse health effects resulting from the use of *ayahuasca* by such naive travelers has recently been expressed by a noted authority on Mestizo

ayahuasca use (Dobkin de Rios, 1994). These concerns are in marked contrast to testimonials of improved psychological and moral functioning by the adherents of the syncretic *ayahuasca* churches in Brazil.

The individuals who are attracted to the UDV seem to belong to a slightly more professional socio-economic class than those who join the Santo Daime. Of the approximately 7000 members of the UDV in Brazil, perhaps 5 - 10 % are medical professionals, among them physicians, psychiatrists, psychologists, chiropracters, and homeopathic physicians. Most of these individuals are fully aware of the psychologically beneficial aspects of the practice, and evince a great interest in the scientific study of *hoasca*, including its botany, chemistry, and pharmacology. The medically educated members can discuss all of these aspects with a sophistication equal to that of any U.S.-trained physician, botanist, or pharmacologist. At the same time they do have a genuine spiritual reverence for the *hoasca* tea and the experiences it evokes. The UDV places a high value on the search for scientific truth, and sees no conflict between science and religion; most members of the UDV express a strong interest in learning as much as possible about how the tea acts on the body and brain. As a result of this unique circumstance, the UDV presents an ideal context in which to conduct a biomedical investigation of the acute and long-term effects of *hoasca.* (In the parlance of the UDV, the tea is sometimes called *hoasca*, which is a Portguese transliteration of *ayahuasca.* The term as used here applies specifically to the tea used within the UDV, while *ayahuasca* is used to denote non-UDV sources of the brew.)

Due to a fortunate combination of circumstances, we were invited to conduct such a biomedical investigation of long-term drinkers of hoasca by the Medical Studies section of the UDV (Centro de Estudos Medicos). This study, which was conducted by an international consortium of scientists from Brazil, the United States, and Finland, was financed through private donations to various non-profit sponsoring groups, notably Botanical Dimensions, which provided major funding, the Heffter Research Institute, and MAPS, (Multidisciplinary Association for Psychedelic Studies). Botanical Dimensions is a non-profit organization dedicated to the study and preservation of ethnomedically significant plants, and MAPS and the Heffter Research Institute are non-profit organizations dedicated to the investigation of the medical and therapeutic uses of psychedelic agents. The field phase of the study was conducted during the summer of 1993 at one of the oldest UDV temples, the Nucleo Caupari located in the Amazonian city of Manaus, Brazil. Subsequent laboratory investigations took place at the respective academic institutions of some of the principle investigators, including the Department of Psychiatry, Harbor UCLA Medical Center, the Department of Neurology, University of Miami School of Medicine, the Department of Psychiatry, University of Rio de Janeiro, Department of Internal Medicine, University of Amazonas Medical School, Manaus, and the Department of Pharmaceutical Chemistry, University of Kuopio, Finland.

Since this study was the first of its kind, there was virtually no pre-existing data on the objective measurement of the physical and psychological effects of ayahuasca in human subjects. As a result, this study was in some respects a pilot study; its primary objectives were modest, representing an effort to collect a basic body of data, without attempting to relate the findings to either possible detrimental effects of ayahuasca, or to possible therapeutic effects. The study had four major objectives:

- Assessment of Acute Psychological and Physiological Effects of *Hoasca* in Human Subjects
- Assessment of Serotonergic Functions in Long-term Users of *Hoasca* Tea
- Quantitative Determination of Active Constituents of *Hoasca* Teas in Plasma
- Quantitative Determination of Active Constituents of *Hoasca* Teas

Most of these objectives were achieved, and the results have been published in various peer-reviewed scientific journals (Grob, et al., 1996; Callaway, et al., 1994; Callaway, et al., 1996;. Callaway, et al., 1997). The results are summarized briefly below.

**Assessment of Acute and Long-term Psychological Effects of Hoasca Teas (Grob, et al., 1996)**

The subjects in all of the studies consisted of a group of fifteen healthy, male volunteers, all of whom had belonged to the UDV for a minimum of ten years, and who ingested hoasca on average of once every two weeks, in the context of the UDV ritual. None of the subjects actively used tobacco, alcohol, or any drugs other than hoasca. For some comparative aspects of the study, a control group of fifteen age-matched males was also used; these individuals were recruited from among the friends and siblings of the volunteer subjects, and like them were local residents of Manaus having similar diets and socio-economic status. None of the control subjects were members of the UDV, and none had ever ingested hoasca tea.

The psychological assessments, administered to both groups, consisted of structured psychiatric diagnostic interviews, personality testing, and neuropsychological evaluations. Measures administered to the UDV hoasca drinkers, but not to the hoasca-niave group, included semistructured and open-ended life story interviews, and a phenomenological assessment of the altered state elicited by hoasca, was quantified using the Hallucinogen Rating Scale developed by Dr. Rick Strassman in his work with DMT and psilocybin in human subjects (Strassman, et al., 1994).

The UDV volunteers showed significant differences from the hoasca-naive subjects in the Tridimensional Personality Questionnaire (TPQ) and the WHO-UCLA Auditory Verbal Learning Test. The TPQ assesses three general areas of behavior,

viz., novelty-seeking, harm avoidance, and reward dependence. With respect to novelty-seeking behaviors, UDV members were found to have greater stoic rigidity vs exploratory excitability, greater regimentation vs disorderliness, and a trend toward greater reflection vs impulsivity; but there was no difference between the groups on the spectrum between reserve and extravagance. On the harm reduction scale, UDV subjects had significantly greater confidence vs fear of uncertainty, and trends toward greater gregariousness vs shyness, and greater optimism vs anticipatory worry. No significant differences were found between the two groups in criteria related to reward-dependence.

The fifteen UDV volunteers and the control subjects were also given the WHO-UCLA Auditory Learning Verbal Memory Test. Experimental subjects performed significantly better than controls on word recall tests. There was also a trend, though not statistically significant, for the UDV subjects to perform better than controls on number of words recalled, delayed recall, and words recalled after interference.

The Hallucinogen Rating Scale, developed by Strassman et. al (1994) for the phenomenological assessment of subjects given intravenous doses of DMT, was administered to the UDV volunteers only (since control subjects did not receive the drug). All of the clinical clusters on the HRS were in the mild end of the spectrum compared to intravenous DMT. The clusters for affect, intensity, cognition, and volition, were comparable to an intravenous DMT dose of 0.1 to 0.2 mg/kg, and the cluster for perception was comparable to 0.1 mg/kg intravenous DMT, and the cluster for somatesthesia was less than the lowest dose of DMT measured by the scale, 0.05 mg/kg.

The most striking findings of the psychological assessment came from the structured diagnostic interviews, and the semi-structured open-ended life story interviews. The Composite International Diagnostic Interview (CIDI) was used for the structured diagnostic interview. None of the UDV subjects had a current psychiatric diagnosis, whereas two of the control subjects had an active diagnosis of alcohol abuse and hypochondriasis. Only one subject among the controls had a past psychiatric disorder that was no longer present; an alcohol abuse disorder that had remitted two years previously. However, prior to membership in the UDV, eleven of the UDV subjects had diagnoses of alcohol abuse disorders, two had had past major depressive disorders, four had past histories of drug abuse (cocaine and amphetamines), eleven were addicted to tobacco, and three had past phobic anxiety disorders. Five of the subjects with a history of alcoholism also had histories of violent behavior associated with binge drinking. All of these pathological diagnoses had remitted following entry into the UDV. All of the UDV subjects interviewed reported the subjective impression that their use of hoasca tea within the context of the UDV had led to improved mental and physical health, and significant improvements in interpersonal, work, and family interactions.

**Assessment of Serotonergic Functions in Long-term Users of Hoasca (Callaway, et al., 1994)**

Another objective of the study was to investigate whether long-term use of hoasca resulted in any identifiable "biochemical marker" that was correlated with hoasca consumption, particularly with respect to serotonergic functions, since the hoasca alkaloids primarily affect functions mediated by this neurotransmitter. Ideally, such a study could be carried out on post-mortem brains of long-term drinkers in comparison to those of non-drinkers. In this study, this ideal could not be attained due to the fact that the subjects were still alive and using their brains! We settled on looking at serotonin transporter receptors in blood platelets as the next best alternative, using [$^3$H]-citalopram to label the receptors in binding assays. The up-or down regulation of peripheral platelet receptors is considered indicative of similar biochemical events occurring in the brain, although there is some controversy about the correlation between platelet receptor changes and changes in CNS receptors medications (Stahl, 1977; Pletscher and Laubscher, 1980; Rotman, 1980). However, platelet receptors were deemed suitable for the purposes of our study, as our objective was not to resolve this controversy but simply to determine if some kind of long-term biochemical marker could be identified. Neither did we postulate any conclusions about the possible "adverse" or "beneficial" implications of such a marker, if detected. We conducted the assays on platelets collected from the same group of 15 volunteers after they had abstained from consuming the tea for a period of three weeks. We also collected platelet specimens from the age-matched controls who were not hoasca drinkers. We were surprised to find a significant up-regulation in the density of the citalopram binding sites in the hoasca drinkers compared to control subjects. While the hoasca drinkers had a higher density of receptors, there was no change in the affinity of the receptors for the labelled citalopram. The significance of this finding, if any, is unclear. There is no other pharmacological agent which is known to cause a similar upregulation, although chronic administration of 5-HT uptake inhibitors has been reported to decrease both Bmax (the density of binding sites) and 5-HT transporter RNA in rats (Hrinda 1987; Lesch et al., 1993). Increases in Bmax for the uptake site in human platelets have been correlated with old age (Marazziti et al, 1989) and also the dark phase of the circadian cycle in rabbits (Rocca et al., 1989). It has been speculated (Marazziti et al, 1989) that upregulation of 5-HT uptake sites in the aged may be related to the natural course of neuronal decline. Although our sample size was limited, we found no correlation with age, and the mean age of the sample was 38 years. Also, none of our subjects showed evidence of any neurological or psychiatric deficit. In

fact, in view of their exceptionally healthy psychological profiles, one of the investigators speculated that perhaps the serotonergic upregulation is associated, not simply with age, but with "wisdom" -- a characteristic often found in the aged, and in many hoasca drinkers.

Another interesting self-experiment related to this finding was carried out by one of the investigators, Jace Callaway, following his return to Finland after the field phase of the study was completed. Dr. Callaway has access to Single Photon Emission Computerized Tomography (SPECT) scanning facilities in the Department of Pharmacology at the University of Kuopio. Suspecting that the causative agent of the unexpected upregulation might be tetrahydroharmine (THH), Dr. Callaway took SPECT scans of his own brain 5-HT uptake receptors prior to beginning a six week course of daily dosing with tetrahydroharmine, repeating the scan after the treatment period. He did indeed find that the density of central 5-HT receptors in the prefrontal cortex had increased; when he discontinued THH, their density gradually returned to previous levels over the course of several weeks. While this experiment only had one subject, if it is indicative of a general effect of THH that can be replicated and confirmed, the implications are potentially significant. A severe *deficit* of 5-HT uptake sites in the frontal cortex has been found to be correlated with aggressive disorders in violent alcoholics; if THH is able to specifically reverse this deficit, it may have applications in the treatment of this syndrome. These findings are especially interesting when viewed in the context of the psychological data collected in the hoasca study (Grob, et al., 1996). The majority of the subjects had had a previous history of alcoholism, and many had displayed violent behavior in the years prior to joining the UDV; virtually all attributed their recovery and change in behavior to their use of hoasca tea in the UDV rituals. While it can be argued that their reformation was due to the supportive social and psychological environment found within the UDV, the finding of this long-term change in precisely the serotonin system that is deficient in violent alcoholism, argues that biochemical factors may also play a role

**Assessment of the Acute Physiological Effects of Hoasca Tea (Callaway, et al., 1997)**

The major focus of the biochemical and physiological measurements carried out for the study was on the acute effects subsequent to consuming hoasca tea. One of the objectives was simply to measure the effects of hoasca on standard physiological functions, such as heart rate, blood pressure, and pupillary diameter, subsequent to ingestion. We found that all of these responses were well within normal parameters. Hoasca, not surprisingly, caused an increase in pupillary diameter from baseline (pre-dose) levels of 3.7 mm to approximately 4.7 mm at 40 minutes, which continued to 240 minutes after ingestion at which point measurements were discontinued. Breaths per minute fluctuated throughout the 240 minutes, from a low of 18.5 at baseline to a high of 23 breaths per minute at 100 minutes. Temperature rose from a baseline low of 37 ° C at baseline to a high of 37.3 °C at 240 min (although the ambient temperature also increased comparably during the course of the experiments, which were conducted from 10:00 - 16:00). Heart rate increased from 71.9 bpm at baseline to a maximum of 79.3 bpm by 20 minutes, decreased to 64.5 bpm by 120 minutes, then gradually returned toward basal levels by 240 minutes. There was a concomitant increase in blood pressure; both systolic and diastolic pressure increased to maxima at 40 minutes (137.3 and 92.0 mm Hg respectively) over baseline values (126.3 and 82.7 mm Hg respectively) and returned to basal values by 180 minutes. We also measured nueroendocrine response for plasma prolactin, cortisol, and grwoth hormone; all showed a rapid and dramatic increases over basal values from 60 minutes (cortisol) to 90 minutes (growth hormone) to 120 minutes (prolactin) after ingestion. The observed response, typical of serotonergic agonists, are comparable to the values reported by Strassman & Qualls (1994) in response to injected DMT. In our study, however, the response to oral DMT was delayed by a factor of four or five. Dr. Russell Poland, of the Harbor-UCLA Medical Center, carried out the neuroendocrine measurements.

**Characterization of the Pharmacokinetics of Hoasca Alkaloids in Human Subjects (Callaway, et al., 1996; 1997)**

The fourth objective of the study was to measure pharmacokinetic parameters of the hoasca alkaloids in plasma following ingestion of hoasca tea, and to correlate this to the amounts of alkaloids ingested. The UDV collaborators held a special "preparo" to prepare the sample of hoasca that was used for all subjects in the study. The mestres confirmed the activity in the usual manner, via ingestion, and pronounced it active and suitable for use in the study. Subsequent analysis by HPLC found the tea to contain, in mg/ml: harmine, 1.7; harmaline, 0.2; THH, 1.07; and DMT 0.24. Each subject received an aliquot of tea equivalent to 2 ml/kg body weight, which was consumed in a single draught. Based on the average body weight (74.2 ± 11.3 kg), the average dose of tea was 148.4 ± 22.6 ml, containing an average of 35.5 mg DMT, 158.8 mg THH, 29.7 mg harmaline, and 252.3 mg harmine. These doses are above the threshold level of activity for DMT as a psychedelic, and for harmine and THH as MAO inhibitors; harmaline is essentially a trace constituent of hoasca tea (Callaway, et al., 1996, 1997).

Only 12 of the 15 volunteers had sufficient plasma levels of DMT to permit pharmacokinetic measurements, possibly due to early emesis during the course of the session. Of these, the maximum plasma concentration (Cmax) (15.8 ng/ml) occurred at 107 minutes after ingestion, while the half-life ($T_{1/2}$

was 259 minutes. THH was measured in 14 of the 15 subjects; the Cmax was 91 ng/ml, reached at 174 min. This compound displayed a prolonged half-life of 532 minutes, in contrast to harmine which had a half-life of 115.6 min. The Cmax for harmine and harmaline was 114.8 and 6.3 ng/ml, respectively, and time of maximum concentration (Tmax) was 102 and 145 minutes, respectively. The $T_{1/2}$ for harmaline could not be measured (Callaway, et al.,1997).

In many ways this study was conceived because of the need to collect some basic data on the physiological and pharmacokinetic characteristics of ayahuasca, since none had previously existed. The conclusions to be drawn from the results, if any, are interesting and potentially significant, particularly in that these findings may offer a physiological rationale for the marked improvements in psychological health that is correlated with long-term hoasca use. Not surprisingly, the highest plasma concentrations of DMT correlated with the most intense subjective effects; however, the psychological measurement (Hallucinogen Rating Scale) indicated that comparable plasma levels of injected DMT in the study by Strassman & Qualls (1994) gave effects that were more intense than those reported from the hoasca tea. One possible explanation is that THH, by acting as a 5-HT reuptake inhibitor, may have resulted in a greater availability of 5-HT at the synapse, and this may have competed with DMT for occupancy at serotonergic synapses.

Another point worthy of remark is that the activity of THH in hoasca is apparently more a function of its inhibition of 5-HT uptake than to its action as an MAOI. THH is a poor MAOI compared to harmine ($EC_{50}$ = 1.4 x $10^{-5}$ M vs 8 x $10^{-8}$ M for harmine), and while the plasma levels for harmine are well above the $EC_{50}$ values, those for THH are well below the $EC_{50}$ value for this compound as an MAOI.

**Future Studies**

The major objectives of the initial biomedical investigation of hoasca have been met, including the overall objective, that of developing a basic body of descriptive information on the physiological and psychopharmacological characteristics of the tea. But, like all good science, these investigations raise more question than they have answered. It seems clear that ayahuasca is relatively safe; it can be taken on a regular schedule for months or even years without producing any adverse effect. Indeed, all of our subjects were highly functional individuals who attribute much of their "coping" skills to the tea and the lessons it has taught them, albeit within the doctrinal context of the UDV. None of them showed any signs of physical disease, or neurological or psychological deficits, indeed, many had higher scores in some of the psychometric testing regimes than comparable control subjects who had never imbibed hoasca. Yet many questions remain, and it is to be hoped that future investigations will be done, and that some of the most relevant questions will be at least partially answered. Among areas which suggest themselves for future research, the following seem obvious:

- **Effect of hoasca on women, particularly pregnant and/or lactating women.** For simplicity's sake, our initial study included only male subjects who had imbibed the tea on a regular basis for at least ten years. Thus our sample was deliberately restricted; it included only experienced hoasca drinkers, and only men, just to minimize the number of variables. But women also drink hoasca, and moreover, most do so throughout pregnancy and lactation; indeed, children in the UDV are baptized with a tiny spoonful of hoasca, although they are not usually exposed to pharmacologically active amounts until at least age 13. There are many issues here worthy of study. For example, women claim that hoasca has positive benefits both in managing their pregnancy, and in assisting birth; many will take hoasca during labor to facilitate the process. The role of hoasca during pregnancy and lactation, whether adverse or positive, is just one of a score of questions which could be answered by follow-up studies using women hoasca drinkers.
- **Prospective studies, with children and new members.** For similar reasons, our study did not include any recent converts to the UDV, nor any children, who, if they choose, are allowed to attend UDV sessions and imbibe smaller amounts of hoasca as early as age 13. Nor did the study include any recent adult converts to the UDV. Clearly, prospective studies of both groups could add a great deal to our knowledge. In view of our finding that hoasca apparently brings about long-term increases in serotonin uptake receptor densities, the implications of this need to be further investigated, and prospective studies may clarify this question. For instance, is the increase in serotonin uptake sites a consequence of regular imbibition of hoasca, as would seem the obvious conclusion, or are hoasca drinkers as a group biased toward those who are predisposed toward naturally high receptor densities? And what are the implications of either finding? Similar questions, as well as a host of sociological and developmental questions, could be addressed in a prospective study of children of UDV members who remain in the group and start to imbibe hoasca regularly in adolescence. An obvious question to answer in this context would be an assessment of children and adolescents who were exposed to hoasca in utero, to determine the impact, if any, of prenatal hoasca exposure on their subsequent neurological and psychological development. Another question germane to the possible long-term health benefits of regular hoasca use is that of whether the practice might prove to be prophylactic against alcohol and drug abuse for adolescents who consume the tea within the UDV structure.

- **Brain imaging and electrophysiological studies** To the degree that facilities can be made available, brain imaging and electrophysiological studies of the acute and chronic effects of hoasca would further fill in the picture of its pharmacological characteristics.
- **Therapeutic applications of hoasca in treatment of substance abuse and alcoholism** The experience of UDV members, recounted in the structured "life-story" interviews, would seem to indicate that hoasca has real potential as a therapeutic agent in treating substance abuse and/or alcoholism as well as other psychopathologies. Most of the subjects interviewed were involved with substance abuse prior to joining the UDV, and have since ceased. Most attribute their recovery to the tea; it would seem that confirmation of their experience and further information could be collected relatively easily, perhaps through a prospective study using recent converts to the UDV having prior involvement with substance abuse or other addictive disorders.
- **Immunomodulatory effects of hoasca** Another parameter that could be easily assessed, that may have important implications for the long-term health effects of hoasca, is the question of its possible effects on the immune system. Hoasca may be an immunostimulant, and thus potentially beneficial in maintaining resistance to disease; on the other hand, it could be an immunosuppressant, and this would also have serious implications for long-term or frequent use. Although hoasca tea is customarily used as a ritual sacrament rather than a medicine, anecdotal reports suggesting that hoasca may facilitate recovery from serious illnesses such as cancer, and well-designed studies are needed to investigate this question. One possibility is that discontinuation of the use of alcohol, tobacco, and drugs of abuse, as is common in UDV members, may contribute to long-term salutary effects on health.

**Summary**

Ayahuasca, or hoasca, whether known by these names, or any of numerous other designations, has long been a subject of fascination to ethnographers, botanists, psychopharmacologists, and others with an interest in the many facets of the human relationship with, and use of, psychoactive plants. With its complex botanical, chemical, and pharmacological characteristics, and its position of prime importance in the ethnomedical and magico-religious practices of indigenous Amazonian peoples, the investigation of ayahuasca in its many aspects has been an impetus to the furtherence of our scientific understanding of the brain/mind interface, and of the role that psychoactive plant alkaloids have played, and continue to play, in the quest of the human spirit to discover and to understand its own trancendent nature.

Now, the process that has unfolded in Western culture since Richard Spruce first reported on ayahuasca use among the Indians of the Norwthwest Amazon in 1855 (Anon, 1855; Spruce, 1873) has reached a new stage. Ayahuasca has emerged from the Amazonian jungles where it has remained cloaked in obscurity for thousands of years, to become the sacramental vehicle for new syncretic religious movements that are now diffusing from their center of origin in Brazil to Europe, the United States, and throughout the world. As the world observes this process unfolding (with joyous anticipation for some, and with considerable trepidation for others), the focus for the scientific study and understanding of ayahuasca has shifted from the ethnographer's field notes and the ethnobotanist's herbarium specimens, to the neurophysiologist's laboratory and the psychiatrist's examining room. With the completion of the first detailed biomedical investigation of ayahuasca, science now has the basic corpus of data needed to ask further questions, regarding the pharmacological actions, the toxicities and possible dangers, and the considerable potential Ayahuasca has to heal the human mind, body, and spirit. Humanity's relationship with ayahuasca is a long-term commitment, expressed on an evolutionary time scale, that has already taught us much, and from which we can still learn much, provided we have the courage, and the tools, to ask the right questions.

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