TESI DOCTORAL

HUMAN PHARMACOLOGY OF *AYAHUASCA*

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Director de la Tesi:

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A la Núria, el Marc i l'Emma.

No pasaremos en silencio una de las cosas que á nuestro modo de ver llamará la atención... toman un bejuco llamado *Ayahuasca* (bejuco de muerto ó almas) del cual hacen un lijero cocimiento...esta bebida es narcótica, como debe suponerse, i á pocos momentos empieza a producir los mas raros fenómenos...Yo, por mí, sé decir que cuando he tomado el *Ayahuasca* he sentido rodeos de cabeza, luego un viaje aéreo en el que recuerdo percibia las prespectivas mas deliciosas, grandes ciudades, elevadas torres, hermosos parques i otros objetos bellísimos; luego me figuraba abandonado en un bosque i acometido de algunas fieras, de las que me defendia; en seguida tenia sensación fuerte de sueño del cual recordaba con dolor i pesadez de cabeza, i algunas veces mal estar general.

Manuel Villavicencio
Geografía de la República del Ecuador (1858)

Das, was den Indianer den “Aya-huasca-Trank” lieben macht, sind, abgesehen von den Traumgesichten, die auf sein persönliches Glück Bezug habenden Bilder, die sein inneres Auge während des narkotischen Zustandes schaut.

Louis Lewin
Phantastica (1927)

Agraïments

La present tesi doctoral constitueix la fase final d'una idea nascuda ara fa gairebé nou anys. El fet que aquest treball sobre la farmacologia humana de l'*ayahuasca* hagi estat una realitat es deu fonamentalment al suport constant del seu director, el Manel Barbanoj. Voldria expressar-li la meva gratitud pel seu recolzament entusiàstic d'aquest projecte, molt allunyat, per la natura del fàrmac objecte d'estudi, dels que fins al moment s'havien dut a terme a l'Àrea d'Investigació Farmacològica de l'Hospital de Sant Pau. L'interès inexhaurible del Dr. Barbanoj per tots els aspectes de la psicofarmacologia humana i la llibertat que m'ha donat al llarg d'aquests anys per dur a terme aquest treball de recerca han estat uns dels principals atractius d'aquesta feina.

No puc oblidar en aquests agraïments als iniciadors de la idea i exploradors de terres incògnites Josep Maria Fericgla i Esther Martínez. A ells dec haver dirigit la meva atenció cap aquest fascinant preparat amazònic. Així mateix, sense la col·laboració inestimable de l'Esther Martínez, el Félix González i el Josep Maria Fàbregas l'*ayahuasca* no hauria arribat mai al nostre laboratori i aquest estudi mai no s'hauria portat a terme. El meu agraïment també als membres de CEFLURIS a Brasil per haver accedit a facilitar les mostres d'*ayahuasca* (*Daime*) que es van emprar a l'estudi clínic.

També estic en deute amb el Francesc Jané, pel seu suport com a cap del Servei de Farmacologia Clínica de l'Hospital de Sant Pau; amb el James C. Callaway, per dur a terme les anàlisi del contingut de DMT de l'*ayahuasca*; amb la Graciela Salazar, per ajudar-me en l'escriptura inicial del protocol de recerca i amb el Rick J. Strassman, per supervisar l'adaptació del qüestionari HRS i per facilitar-me les dades de farmacocinètica obtingudes al seu estudi d'administració intravenosa de DMT. El meu agraïment a la Gloria Urbano per la seva amistat incondicional en moments difícils i per les llargues hores que vam compartir durant la fase experimental de l'estudi. Gràcies al Toni Rodríguez, sobretot per fer-me de mestre en l'adquisició i processament dels registres neurofisiològics; al Peter Anderer, pel seu paper fonamental en la quantificació de les dades d'EEG i LORETA i a la Marta Valle, per la seva col·laboració en l'estudi i interpretació de les dades cinètiques.

El meu reconeixement també per la Mercedes Yritia, l'Araceli Castillo i la Yolanda Alfaro del laboratori d'anàlisi pel seu esforç en la determinació de les β-carbolines (tantes) i al Rafael de la Torre i al Jordi Ortuño del laboratori d'anàlisi de l'IMIM per la determinació de la DMT. Gràcies al Magí Farré, també de l'IMIM, per tota la informació facilitada directa o indirectament sobre les tècniques de mesura dels efectes subjectius dels fàrmacs i al Josep Maria Queraltó del Servei de Bioquímica de Sant Pau per la determinació del metabolits de les monoamines. Als companys del CIM, particularment a l'Adelaida Morte, la Susanna Clos, la Llúcia Benito, el David Martínez i la Sylvie Cotxet, per la seva col·laboració en la recollida de les dades experimentals. A l'Ángeles Funes i el Pablo Ayesta per la seva ajuda en l'edició dels manuscrits i a la Carolyn Newey per les seves pacients i exhaustives revisions de l'anglès.

Finalment estaré eternament agraït als meus avis, pares i germana per fer-me la vida molt més amable i a la Núria per haver estat sempre al meu costat tot aquest temps.

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INTRODUCTION

1. Early reports on *ayahuasca*, its botanical sources and uses

Ayahuasca is the Quechua name used to designate a traditional psychotropic plant beverage widely used by the indigenous peoples of northwestern South America. The area of use has been estimated to extend from Panama to Amazonian Peru and Bolivia and from the coastal areas of Colombia and Ecuador to the Río Negro in Brazil (Ott, 1993). While the term *ayahuasca*, which also designates the plant the beverage is made from, is used in Peru and some areas of Ecuador and Colombia, this psychotropic tea is also known by many other vernacular names. The term *caapi* is employed in the river Vaupés, *yajé* or *yagé* in southern Colombia, *Daime* or *Hoasca* in Brazil, *natema* in Ecuador and *pinde* along the Pacific coast of Colombia. More than 70 indigenous groups are known to employ *ayahuasca*, for which 42 different vernacular names have been reported (Luna, 1986). The use of this pan-Amazonian psychotropic beverage appears to be very old, since according to Plutarco Naranjo, several pottery artifacts which could have been used for *ayahuasca* preparation/ingestion date back to 2000–1000 B.C. (Naranjo, 1986). Oddly enough, *ayahuasca* use had apparently remained unknown by the outside world until very recent times. Despite the fact that European exploration of the Amazon had taken place as early as 1541, the first written reference to its use was made well into the 18th century by Jesuit priests travelling through the region (Naranjo, 1986). This is in sharp contrast with the ritual use of other visionary plants and preparations such as peyote and the *cohoba* snuff which had been known to the Spaniards since the early days of their arrival in the New World (Sahagún, 2001; Wassen, 1967).

The plant source of *ayahuasca* was first described in the 19th century. In 1852, the English botanist Richard Spruce observed the use of a "climbing plant" called *caapi* as an intoxicant by Tukanoan tribes in the Vaupés river in northwestern Brazil, and characterized the plant as an undescribed *Banisteria* of the Malpighiaceae family. Spruce named it *Banisteria caapi* (see Figure 1) and collected specimens for posterior chemical analysis, which would not be conducted until more than a hundred years later. He also described a communal celebration in which *caapi* was served and commented on the effects exerted by the brew (Spruce, 1908):

> In two minutes or less after drinking it, its effects begin to be apparent. The Indian turns deadly pale, trembles in every limb, and horror is in his aspect. Suddenly contrary symptoms succeed: he bursts into a perspiration, and seems possessed with reckless fury, seizes whatever arms are at hand, his murucú, bow and arrows,

> or cutlass, and rushes to the doorway, where he inflicts violent blows on the ground or the doorposts, calling out all the while, 'thus would I do to mine enemy (naming him by his name) were this he!' In about ten minutes the excitement has passed off, and the Indian grows calm, but appears exhausted.

Spruce partook of *ayahuasca* but all he experienced was a "strong inclination to vomit". However, he further commented that travelers he had talked to had experienced rather remarkable effects:

> Alternations of cold and heat, fear and boldness. The sight is disturbed, and visions pass rapidly before the eyes, wherein everything gorgeous and magnificent they have heard or read of seems combined; and presently the scene changes to things uncouth and horrible…intelligent traders on the Upper Rio Negro, Uaupés and Orinoco have all told me the same tale, merely with slight personal variations. A Brazilian friend that when he took a full dose of *caapi* he saw all the marvels he had read of in the Arabian Nights pass rapidly his eyes as in a panorama; but the final sensations and sights were horrible, as they always are.

Two years later, Spruce observed the use of *caapi* in the Orinoco by the Guahibo Indians who drank the infusion and also chewed the dried stem. Again, in 1857 in the foothills of the Andes in the area of the river Pastaza in Ecuador he saw *caapi* was cultivated by the Záparo Indians, although it was known under the name *ayahuasca*, meaning "Dead man's vine".

Spruce's contemporary, the Ecuadorian geographer Manuel Villavicencio, commented on the use of a vine by the Záparo, Angatero, Mazán and other tribes of the Río Napo region and wrote an account of his own experience with *ayahuasca*. According to Villavicencio (1858), the vine was used:

> To foresee and to answer accurately in difficult cases, be it to reply opportunely to ambassadors from other tribes in a question of war; to decipher plans of the enemy through the medium of this magic drink and take proper steps for attack and defense; to ascertain, when a relative is sick, what sorcerer has put on the hex; to carry out a friendly visit to other tribes; to welcome foreign travelers; or, at least, to make sure of the love of their womenfolk.

Villavicencio goes on:

> When I have partaken of aya-huasca, my head has immediately begun to swim, then I have seemed to enter on an aerial voyage, wherein I thought I saw the most charming landscapes, great cities, lofty towers, beautiful parks, and other delightful things. Then all at once I found myself deserted in a forest and attacked by beasts of prey, against which I tried to defend myself. Lastly, I began to come around, but with a feeling of excessive drowsiness, headache and sometimes general malaise.

The description of the botanical species identified by Spruce was first published by Grisebach, and years later Morton revised the plant's classification and found it to belong to the genus *Banisteriopsis* rather than *Banisteria*. The plant's current botanical name is *Banisteriopsis caapi* (Spruce ex. Griseb.) Morton. Two species of *Banisteriopsis, B. inebrians* Morton and *B. quitensis* (Nied.) Morton, formerly considered independent species also used in the preparation of the Amazonian psychotropic tea, are now considered to be synonyms of *B. caapi*. Other *Banisteriopsis* species reportedly used in the elaboration of *ayahuasca* are *B. martiniana*, *B. muricata*, *B. longialata* and *B. lutea* (Ott, 1993). Descriptions of the actual procedure used in the obtention of *B. caapi* extracts indicate variations from one geographical location to the other. Large pieces or cuttings of intact or pounded vine are used in the preparation of the tea, which in the Colombian Amazon is essentially a cold-water extract (Schultes and Raffauf, 1992), while in other geographical areas various degrees of cooking and concentration of the resulting brew have been described. Thus, while in the Purús river area in Peru brief boiling for 1 hour is used with no further processing (Rivier and Lindgren, 1972), in Pucallpa, also in Peru, a 10-15 h cooking period is followed by concentration of the tea. The latter process leads to much higher levels of active compounds being extracted (McKenna et al., 1984).

A relevant aspect of *ayahuasca*'s botany and pharmacology is the widespread practice of using a large number of plants as additives to the tea. This has caused some confusion regarding the botanical identity of *ayahuasca*, since the basic ingredient, *B. caapi*, and the tea derived from it are usually designated with the same name, irrespective of the admixture plants used. Furthermore, some plants added to the brew display potent psychotropic activity on their own, which has led several authors to confuse, for instance, species of *Brugmansia*

with *ayahuasca*. Another common error has been the identification of the apocynaceous *Prestonia amazonica* as the source of *yajé* (Schultes and Hoffman, 1980). Usual admixtures to *ayahuasca* are tobacco (*Nicotiana* spp.), coca (*Erythroxylum coca*), *Ilex guayusa*, several species from the solanaceae family such as *Brugmansia* spp. and *Brunfelsia* spp. and many others, totaling 90 different species belonging to 38 families (Ott, 1993). Among the most commonly used additives are the leaves of *chacruna*, the rubiaceous *Psychotria viridis* Ruiz & Pavón (see Figure 2) and the leaves of *oco-yajé* or *chagropanga*, the malpighiaceous *Diplopterys cabrerana* (Cuatrec.) B. gates, formerly known by the basionyms *Banisteriopsis rusbyana* (Nied.) Morton and *Banisteriopsis cabrerana* Cuatrec. (Schultes and Raffauf, 1992). *Psychotria viridis* is a shrub from the coffee family and is commonly used in Brazil, Peru and Ecuador, whereas *Diplopterys cabrerana* is a liana belonging to the same family as *B. caapi*, used mainly in Ecuador and Colombia (Schultes and Hofmann, 1980; McKenna et al., 1984). As will be discussed below, *ayahuasca* brews incorporating *chacruna* or *chagropanga* are thought to induce their visionary effects through the action of indole alkaloids present in the leaves of these admixture plants.

Figure 1: *Banisteriopsis caapi*. Photo courtesy of Josep Maria Fericgla.

Figure 2: *Psychotria viridis*. Photo courtesy of James C. Callaway

The traditional patterns of use of *ayahuasca* have been extensively researched by anthropologists. Despite varying degrees of acculturation, *ayahuasca* use still survives among the indigenous peoples who inhabit the Amazon Basin. Like many other psychotropic plants of the New World, *ayahuasca* brews are considered sacred and are usually employed by medicine men or shamans for the visionary experiences they elicit. Additionally, other members of the group may ingest the tea in specific ritual ceremonies, such as rites of passage, funerals or communal celebrations (Reichel-Dolmatoff, 1990). Dobkin de Rios (1984) has reviewed the anthropological literature and has summarized the following roles for *ayahuasca* in traditional indigenous societies: 1) as a means to contact the supernatural world, practise divination or witchcraft; 2) as a means to determine the causes of disease and cure the ill; and 3) as a means to obtain pleasure, facilitate sexual activity or social interaction. The following examples can be mentioned: the Jívaro or Shuar of Ecuador have been reported to use *natema* to contact the spirit world to obtain guidance (Fericgla, 1994; Karsten, 1935, cited in Dobkin de Rios, 1984); it has been used both to bring harm to others and for protection against the ill will of others (Fericgla, 1994; Harner, 1972); the Cubeo of Colombia have been known to use *ayahuasca* to achieve pleasurable ecstatic states (Goldman, 1963, cited in Dobkin de Rios, 1984); the Záparo of Ecuador reportedly use it to obtain insight into the future and for healing purposes (Reinburg, 1921, cited in Dobkin de Rios, 1984); and the Peruvian Cashinahua drink *nixi pae* "to learn of things, persons and events removed from them by time and/or space", and their shamans use it to consult the spirits concerning the

causes of someone's illness (Der Marderosian et al., 1970). Rivier and Lindgren mention *ayahuasca* use among the Sharanahua and Culina in Peru both for medical and social purposes (Rivier and Lindgren, 1972). Besides, they comment on the prohibition of *ayahuasca* use for women and children, a restriction also found in the Colombian and Ecuadorian Amazon (Reichel-Dolmatoff, 1990; Villavicencio, 1858).

Today, the use of *ayahuasca* is expanding beyond its original home in the South American rainforest to reach the urban areas of the continent. Around cities like Iquitos in Peru, mestizo folk healers known as *ayahuasqueros* or *vegetalistas* treat the emotional and psychological illnesses of their patients by means of *ayahuasca* sessions (Luna, 1984a; Dobkin de Rios, 1996). These healers use *ayahuasca* visions to diagnose the magic causes of disease or neutralize the evil magic responsible for certain types of illness. *Ayahuasqueros* themselves undergo an apprenticeship during which they observe strict diets and ingest *ayahuasca* and other psychotropic plants such as tobacco (Dobkin de Rios, 1984). Some researchers have emphasized the role of plants as "teachers" in the learning process of the future shaman. The initiate learns certain healing procedures directly from the plant. These can typically include certain magical melodies called "ícaros", that will later be used to combat the evil spirits responsible for illness (Luna, 1984a; Luna, 1984b). It is worth commenting that in the context of Indian and mestizo shamanism, *ayahuasca* does not seem to be used as a curative agent in itself but rather a means used by healers to deal with the supernatural causes of their patient's afflictions.

Another important cultural transformation of *ayahuasca* use is that which has taken place within the so-called *ayahuasca* churches in Brazil. These groups have blended Christian and/or Afro-Brazilian religious beliefs with the indigenous use of *ayahuasca*, which is consumed as a sacrament in the rituals (for a review see the book *O Uso Ritual da Ayahuasca* edited by Labate and Araújo). The oldest of these cults, the *Santo Daime* was founded by a former *seringueiro* or rubber tapper called Raimundo Irineu Serra. Mestre Irineu, as he is known by his followers, was initiated into *ayahuasca* in the 1920s in the jungle regions of Acre state close to the border with Bolivia and Peru (Fróes, 1986; McRae, 1998). During his experiences with *ayahuasca* he had revelations from a female entity, Nossa Senhora da Conceição or Rainha da Floresta, and around 1945 he founded the Centro de Iluminação Cristã Luz Universal (CICLU), also known as Alto Santo in Rio Branco, Acre. The name given to *ayahuasca*, *Daime*, was revealed to Irineu by the Rainha da Floresta and derives

from invocations such as "Dai-me amor, luz força" used in the rituals. The *Santo Daime* doctrine is recopilated in a series of hymns revealed to Mestre Irineu and other members of the church under the effects of *Daime* and sung during the ceremonies. It is essentially dualistic, with the ingredients of *ayahuasca*, i.e., *B. caapi,* known as *cipó*, *mariri* or *jagube,* representing masculinity and *P. viridis* or *folha*, *rainha* or *chachrona* representing femininity. Several groups originated from the original Alto Santo such as the Centro Ecléctico de Correntes da Luz Universal (CECLU) in Porto Velho, Rondônia, or the group led by Sebastião Mota de Melo, Padrinho Sebastião, a follower of Mestre Irineu, who split with the original Alto Santo and founded the Colônia 5000. The group at the Colônia 5000 originally incorporated the use of *Cannabis* in its rituals, leading to a police raid in 1981. Two years later, Padrinho Sebastião's group moved to a more remote location on the river Igarapé do Mapiá, a tributary of the Purús river, and founded the Céu do Mapiá. In 1982, the Céu do Mar was founded outside the jungle, in Rio de Janeiro. In 1989, the *Santo Daime* church adopted the denomination *Centro Ecléctico da Fluente Luz Universal Raimundo Irineu Serra* or CEFLURIS, led by Padrinho Sebãstiao's son, Padrinho Alfredo. In 1998 the church adopted its present name *Igreja do Culto Eclético da Fluente Luz Universal*.

Independently, Daniel Pereira de Matos founded the *Barquinha* in Acre in 1945, and in 1961 José Gabriel da Costa, also a *seringueiro*, established what is today the largest of the *ayahuasca* churches, the *Centro Espírita Beneficente União do Vegetal* (UDV) in Porto Velho, Rondônia. During the 1970s and 80s, both the UDV and the *Santo Daime* spread to the urban centers of southeast Brazil, while the *Barquinha* remained in Acre. The use of *ayahuasca* was temporarily banned in 1985 and after an official governmental investigation of the UDV and the *Santo Daime* the ban was lifted in 1987, an action which effectively legalized the use of *ayahuasca* within a ritual context in Brazil.

In recent years, the *ayahuasca* churches have exported their activities to other countries, contributing to the spread of *ayahuasca* use in the highly industrialized countries of Europe and North America. This phenomenon has been facilitated by the growing interest of many individuals interested in shamanic practices, and also by the fame of *ayahuasca* as a means to facilitate self-knowledge and introspection. Groups of *Santo Daime* and UDV followers have arisen in several European countries, including Germany, Great Britain, Holland, France and Spain as well as in the United States (Anonymous, 2000). Thus, individuals with a very different cultural background to that of the people from Amazonia have come into contact

with the ancient psychotropic beverage in rituals virtually open to all. Furthermore, in this ritual context *ayahuasca* sessions are typically held every 15 days, an unprecedented high frequency of use, and although the number of users is still relatively small outside of Brazil, *ayahuasca* use has raised concerns for public health (Callaway and Grob, 1998). The gradual increase of *ayahuasca* imports into Europe and North America recently attracted the attention of health and police authorities, which led to confiscation of tea shipments, arrests and trials of members in the Netherlands, France, Germany and Spain. In the course of these judicial processes it became evident that both prosecutors and the defense lacked accurate information on the nature of *ayahuasca* brews and on its effects in humans.

2. Chemical constituents of *ayahuasca*

The chief component of *B. caapi's* alkaloidal fraction and the first of its alkaloids to be identified is harmine, a β-carboline which was isolated from *Banisteriopsis* specimens by several researchers working independently. In 1905, the Colombian explorer Zerda Bayon wrote a report on the use of yagé on the Caquetá river and attempted to isolate the active principle from the brew. Although he could not obtain a crystalline compound, a crude precipitate appeared after addition of alkaline salts to the brew. This suggested the presence of an alkaloid he tentatively named telepathine (Perrot and Raymond-Hamet, 1927a). In 1923 Fisher Cardenas apparently isolated an alkaloid in crystalline form for which he conserved the name of telepathine (Perrot and Raymond-Hamet, 1927a), and in 1925 Barriga Villalba published the isolation of two crystalline alkaloids from the stems of yajé, which he erroneously thought to be the species *Haemodictyon amazonicum*. He named the alkaloids yajeine and yajenine (Barriga Villalba, 1925). Perrot and Raymond-Hamet (1927b) isolated telepathine from authentic *Banisteriopsis caapi* and Louis Lewin obtained an alkaloid he named banisterine from a specimen of *Banisteriopsis caapi* and described its pharmacological effects in animals and in human subjects (Lewin, 1928). In the same year, at the pharmaceutical company Hoffman-La Roche, Elger published a paper in which he described the obtention of harmine from a sample of the yagé liana provided by Raymond-Hamet (Elger, 1928). Elger found that the alkaloid in his yagé sample was identical to harmine from *Peganum harmala* and to the telepathine obtained by Perrot and Raymond-Hamet. Wolfes and Rumpf at Merck (1928) reported to have unexpectedly obtained harmine from a Colombian malpighiaceous liana, which was supposed to contain Villalba's yajeine. In 1939, Chen and Chen were able to obtain harmine from the stems, leaves and roots of *B. caapi* and

concluded that telepathine, yajeine and banisterine were the same compound, i.e., harmine. They consequently proposed that the other names given to harmine should be dropped (Chen and Chen, 1939). Years later, Hochstein and Paradies (1957) corroborated and extended these findings with the isolation of harmine, harmaline and *d*-tetrahydroharmine (*d*-THH) from *B. caapi*.

More recent analyses have verified the presence in *B. caapi* of *β*-carboline alkaloids, mainly harmine and *d*-THH, and to a lesser extent harmaline and traces of harmol and harmalol (McKenna et al., 1984; Rivier and Lindgren, 1972). Minor amounts of harmine-*N*-oxide, harmic acid methyl ester and harmalinic acid have been isolated (Hashimoto and Kawanishi, 1975) and in a later study, harmic amide, acetyl norharmine and ketotetrahydronorharmine have been identified (Hashimoto and Kawanishi, 1976). These same authors have also isolated other alkaloids which do not posses the *β*-carboline but the pyrrolidine skeleton: shihunine and dihydroshihunine (Kawanishi et al., 1982).

As mentioned beforehand, other psychoactive plants are frequently added to *ayahuasca* brews. Common admixtures are the nicotine-containing *Nicotiana tabacum* and *Nicotiana rustica*, *Erythroxylum coca* containing ecgonine alkaloids such as cocaine, *Ilex guayusa* and *Paullinia yoco*, both rich in caffeine, the solanaceous *Brugmansia sauveolens* and *Brugmansia insignis* which contain tropane alkaloids like atropine and scopolamine, and many others (Ott, 1993). Among the most commonly used are, however, the tryptamine-containing plants *Psychotria viridis* and *Diplopterys cabrerana* (formerly *Banisteriopsis rusbyana*). These plants are known to be rich in methylated tryptamines. Der Marderosian et al. (1970) found the psychedelic indole *N*,*N*-dimethyltryptamine (DMT) in the leaves of an unidentified species of *Psychotria* used as an *ayahuasca* admixture. Rivier and Lindgren (1972) found DMT in the leaves of *P. viridis* plus trace amounts of *N*-methyltryptamine (NMT) and 2-methyl-1,2,3,4-tetrahydro-*β*-carboline (MTHβC), and McKenna et al. (1984) also found DMT to be the major alkaloid in the leaves of *P. viridis*. The leaves of *D. cabrerana* are also rich in DMT (Agurell et al., 1968; Der Marderosian et al., 1968; Poisson, 1965); in this plant, trace amounts of *N*-methyltryptamine (NMT), 5-Methoxy-*N*,*N*-dimethyltryptamine, 5-hydroxy-*N*,*N*-dimethyltryptamine and *N*-methyltetrahydro-*β*-carboline have also been found (Agurell et al., 1968). Figure 3 shows the chemical structure of the major alkaloids found in *B. caapi, P. viridis* and *D. cabrerana.*

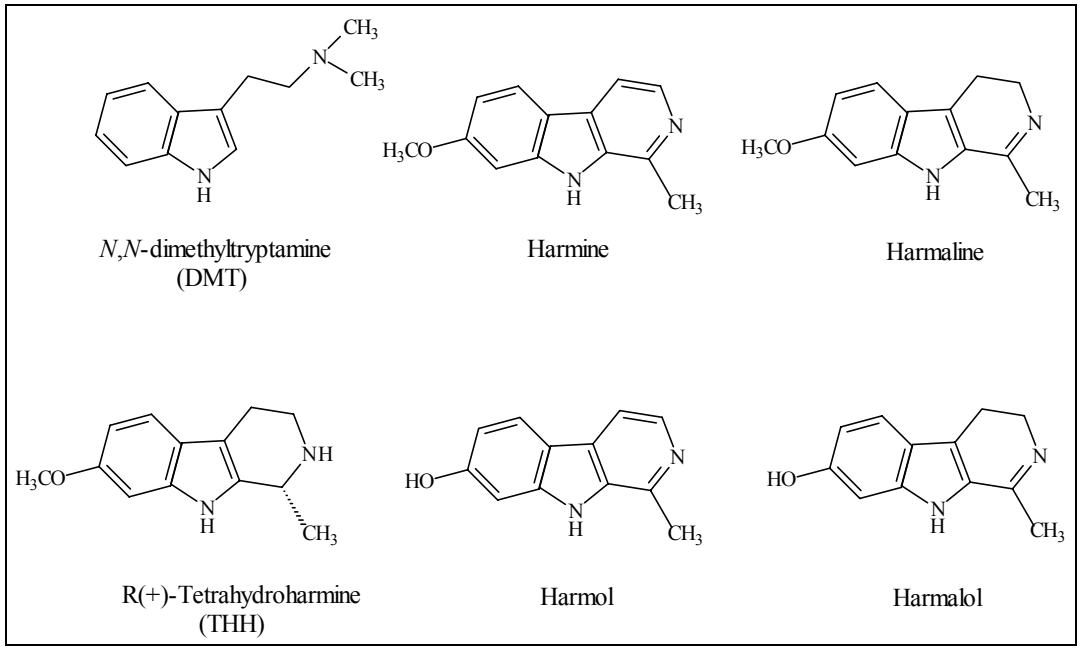

Figure 3: Chemical structures of the main alkaloids found in *Psychotria viridis* and *Diplopterys cabrerana* (*N*,*N*-dimethyltryptamine), and *Banisteriopsis caapi* (harmine, harmaline, THH, harmol and harmalol).

Quantitative Analyses of *Banisteriopsis* have shown the stems to contain an average of 0.4% dry weight of alkaloids, ranging from 0.05% to 1.36%, of which around two thirds are harmine (see Table 1). Other parts of the plant also contain alkaloids, in even higher concentrations. Rivier and Lindgren report 1.95% in the roots of one specimen of *B. caapi* and 1.9% in the leaves of another. However, the roots and leaves of *B. caapi* are rarely used in the preparation of the tea. The alkaloid content in the leaves of *Psychotria* is on average 0.3% (see Table 2), most of it DMT, although in some cases no alkaloids have been found at all, as for instance in a specimen of *Psychotria carthaginensis* Jacq. analyzed by McKenna et al. (1984). The leaves of *Diplopterys cabrerana* contain an average of 0.7% of alkaloids (see Table 2).

Table 1: Alkaloid contents of *Banisteriopsis caapi* dry stems. Figures indicate mean percentage (range).

	Harmine	Harmaline	*d*-THH	Harmol	Harmalol	Total
Hochstein & Paradies, 1957[a]	0.30	trace	trace	n.d.	n.d.	0.30
Poisson, 1965[b]	0.21	trace	n.d.	n.d.	n.d.	0.21
Rivier & Lindgren, 1972[c]	0.25 (0.04-0.51)	0.02 (0.00-0.06)	0.08 (0.00-0.31)	trace	n.d.	0.36 (0.05-0.83)
McKenna et al., 1984[d]	0.39 (0.06-0.64)	0.19 (0.05-0.38)	0.15 (0.03-0.33)	0.04 (0.001-0.12)	0.006 (0.00-0.35)	0.78 (0.17-1.36)

[a] 1 sample collected on the Napo river near Iquitos, Peru; [b] 1 sample collected on the Marañón river, Peru; [c] 14 samples from the Purús river, Peru and other origins; [d] 6 samples collected on different locations in Peru. n.d. = not determined

Table 2: DMT contents of the leaves of *Psychotria* spp. and *Diplopterys cabrerana*, both used as admixtures to *ayahuasca*.

	Species	DMT (%)	
		Mean	Range
Poisson, 1965[a]	*Diplopterys cabrerana*	0.64	---
Der Marderosian et al., 1968[b]	*Diplopterys cabrerana*	1.46	1.33-1.75
Agurell et al., 1968[c]	*Diplopterys cabrerana*	0.47	---
McKenna et al., 1984[d]	*Diplopterys cabrerana*	0.17	---
Der Marderosian et al., 1970[e]	*Psychotria spp.*	0.19	0.17 - 0.22
Rivier & Lindgren, 1972[f]	*Psychotria viridis*	0.17	0.00 - 0.34
Rivier & Lindgren, 1972[g]	*Psychotria carthaginensis*	0.66	---
McKenna et al., 1984[h]	*Psychotria viridis*	0.13	0.10 - 0.16
McKenna et al., 1984[i]	*Psychotria carthaginensis*	0.00	---

[a] 1 sample collected on the Marañón river, Peru; [b] 1 sample collected in eastern Ecuador; [c] 1 sample provided by H. Pinkley. Place of collection not specified; [d] 1 sample collected in Tarapoto, Peru; [e] 4 samples collected at Balta, upper Purús river, southeastern Peru; [f] 2 samples collected on the Purús river, Peru; [g] 1 sample collected on the Purús river, Peru; [h] 3 samples collected in Iquitos, Tarapoto and Pucallpa in Peru. [i] 1 sample collected in Tarapoto, Peru.

The most complete quantitative analyses of *ayahuasca* brews and their plant constituents are those undertaken by Rivier and Lindgren (1972) and McKenna and coworkers (1984). Rivier and Lindgren (1972) studied *ayahuasca* use among the Sharanahua and Culina Indians living on the river Purús in Peru and found that the brew was prepared from *B. caapi* plus *P. viridis* and that on some occasions *P. carthaginensis* was used instead of *P. viridis*. The chemical analyses of 14 samples of stems of authentic *B. caapi* and undetermined *Banisteriopsis* spp. from river Purús and other origins detected a mean alkaloid concentration of 0.36% (range: 0.05-0.83), constituted by the *β*-carbolines: harmine, harmaline, THH and harmol, and also by a tryptamine, 6-methoxytryptamine. Of the total alkaloids, harmine represented on average 74% (range: 42-96), THH represented 16% (range: 1-47) and harmaline 4% (range: 0-9). Harmol and 6-methoxytryptamine were trace constituents found in the stems of four and three samples, respectively. The analyses of *P. viridis* leaves showed the presence of DMT, NMT and traces of MTHβC. Alkaloids represented 0.23% (range: 0.11-0.34) of the dry weight of *P. viridis* and 0.66% of the dry weight of *P. carthaginensis*. Of the total alkaloids, DMT represented 99% in a sample of *P. viridis* and also 99% in a sample of *P. carthaginensis*. One of the two samples of *P. viridis* analyzed was found to be devoid of DMT. Instead, NMT acounted for 85% of the total alkaloids and MTHβC for another 12%. Four other *Psychotria* species: *P. bacteriophylla*, *P. emetica*, *P. undulata* and another not identified were found to be devoid of alkaloids. Analyses of 9 brew samples prepared by the Sharanahua, Culina and Piro tribes combining *Banisteriopsis* sp. and *Psychotria* sp. found a mean alkaloid content of 0.04% (range: 0.01-0.06) consisting of harmine 39% (range: 21-62%), THH 15% (range: 6-40), harmaline 2% (range: 0-4) and DMT 20% (range: 0-41).

McKenna et al. (1984) performed chemical analyses of 6 samples of authentic *B. caapi* collected in Tarapoto, Iquitos and other locations in Peru and found a mean alkaloid concentration in the stems of 0.78% (range: 0.17-1.36), made up of the following *β*-carbolines: harmine, harmaline, THH, harmol and also harmalol in one of the specimens. Of the total alkaloids, harmine represented on average 48% (range: 34-72), THH was 22% (range: 13-47) and harmaline 26% (range: 15-44), while harmol represented only 4% (range: 0.4-9%). The analyses of three specimens of *Psychotria viridis* used as admixtures showed the presence in the leaves of only DMT, except in one sample where traces of MTHβC were detected. Average alkaloid content was 0.13% (range: 0.10-0.16) of the dry weight. A sample of *P. carthaginensis* was found to be devoid of alkaloids. One sample of *Diplopterys*

cabrerana collected previously (in 1976) found 0.17% DMT plus traces of 5-OH-DMT. McKenna and coworkers (1984) performed qualitative analyses of eight *ayahuasca* brew *s*amples collected in the areas around the Peruvian cities of Iquitos, Pucallpa and Tarapoto. The samples studied had been prepared by local *ayahuasqueros* from *B. caapi* plus *P. viridis* and in one case *P. carthaginensis* was used instead of *P. viridis*. The qualitative analyses showed harmine, harmol, harmaline and THH in all samples. Harmalol was detected in one sample. All samples showed DMT except the *ayahuasca* prepared from *P. carthaginensis* which was devoid of this compound. Quantitative analyses of 5 brew samples prepared by Pucallpa *ayahuasqueros* combining *B. caapi* and *P. viridis* showed a mean alkaloid content of 0.73% (range: 0.59-0.82) consisting of harmine 65% (range: 53-67), THH 22% (range: 18-30), harmaline 6% (range: 5-6) and DMT 8% (range: 6-11). Interestingly, some of the *ayahuasca* samples collected by these researchers were freeze-dried and the alkaloid content was quantified in terms of mg/g freeze-dried material. The obtained concentrations are shown in Table 3 together with those found in the *Daime* batch used in the present work.

Table 3: Alkaloid concentrations in freeze-dried *ayahuasca* in mg/g expressed as mean (range).

	Harmine	**Harmaline**	***d*-THH**	**DMT**	**Total Alk.**
McKenna et al., 1984 [a]	23.8 (8.6-57.6)	5.1 (4.2-6.3)	11.1 (8.0-25.5)	6.4 (0.0-7.2)	46.9 (29.1-75.6)
Riba et al., 2001[b]	14.1	1.0	11.4	8.3	34.8

[a] 5 samples of Peruvian *ayahuasca* from Pucallpa, Iquitos and Tarapoto; [b] 1 sample Brazilian *Daime* used in this work

Other authors have also quantified the alkaloid contents in *ayahuasca* brews. The average values reported are shown in Table 4. Average values for DMT range from 0.14 to 1.18 mg/ml, with a mean of 0.48 mg/ml (0.05%). Average values for total β-carbolines range from 0.18 to 6.68 mg/ml with a mean of 2.68 mg/ml (0.27%). Based on the average values reported, the β-carbolines in *ayahuasca* brews represent roughly 76% of the total alkaloids (range: 55-92) and DMT the remaining 24% (range: 8-45). Among the β-carbolines, harmine represents around 44% of the total alkaloids (range: 23-64), THH around 25% (range: 22-41) and harmaline around 7% (range: 0-32).

Table 4: Alkaloid concentrations in *ayahuasca* brews expressed in mg/ml.

	Harmine	Harmaline	*d*-THH	*β*-carbolines*	DMT
Der Marderosian, 1970[a]	0.07	0.11	n.d.	0.18	0.14
Rivier & Lindgren, 1972[b]	0.15	trace	0.05	0.20	0.13
McKenna et al., 1984[c]	4.67	0.41	1.60	6.68	0.60
Liwszyc et al., 1992[d]	1.49	trace	1.39	2.88	0.53
Callaway et al., 1999[e]	1.70	0.20	1.07	2.97	0.24
Callaway, 1999[f]	2.25	0.13	1.82	4.20	1.18
Riba et al., 2001[g]	0.90	0.06	0.72	1.68	0.53

*β-carbolines = harmine + harmaline + *d*-THH; [a] 2 samples of Peruvian *nixi pae*; [b] 9 samples of Peruvian *ayahuasca*; [c] 5 samples of Peruvian *ayahuasca* from Pucallpa; [d] 1 sample of Brazilian *Daime*; [e] 1 sample of Brailian *Hoasca*; [f] 20 samples of Brazilian *Hoasca*; [g] 1 sample of Brazilian *Daime* used in this work. n.d. = not determined

Table 5 lists alkaloid amounts in typical doses. Those studies not clearly reporting their estimate of a typical dose have not been included. Thus, the mean volume of an *ayahuasca* dose is 166 ml (range: 60-237) and involves the ingestion of 193 mg of alkaloids (range: 65-437). Of these, roughly 161 (range: 40-401) correspond to the *β*-carbolines: 109 mg (range: 17-280) harmine, 35 mg (range: 0-96) THH, and 17 mg (range: 0-26) harmaline. Additionally, each dose contains an average of 31 mg (range: 25-36) DMT. However, the total alkaloid intake may be considerably higher in practice, considering that in the course of an *ayahuasca* session several doses are commonly ingested.

Table 5: Alkaloid amounts in mg ingested in reported typical *ayahuasca* doses.

	Harmine	Harmaline	*d*-THH	*β*-carbolines*	DMT
Der Marderosian, 1970[a]	17	26	n.s.	43	33
Rivier & Lindgren, 1972[b]	30	trace	10	40	25
McKenna et al., 1984[c]	280	25	96	401	36

*β-carbolines = harmine + harmaline + *d*-THH; [a] Estimated in 237 ml (8 ounces); [b] Estimated in 200 ml; [c] Estimated in 60 ml;.

Ayahuasca brews thus appear to be composed of two main alkaloid groups, tryptamines, whose main representative in the tea is DMT, and *β*-carbolines, mainly harmine. As was soon

realized by early researchers, *ayahuasca* combines a powerful visionary compound, DMT, with potent enzymatic inhibitors, the *β*-carbolines. As will be discussed in section 8, *ayahuasca* is thought to owe its psychotropic properties to the pharmacological interaction between these two alkaloid classes.

3. Pharmacology of DMT in humans

DMT had already been obtained as a synthetic product by Manske (1931) when it was isolated as the *N*-oxide from the seeds of *Anadenanthera peregrina* (referred to as *Piptadenia peregrina*, Fish et al., 1955a), the putative source of a Piaroa psychotropic snuff. Today, DMT is known to occur in over fifty plant species (Ott, 1994) and to be a major active component of *ayahuasca* and other psychotropic plant preparations. The presence of DMT in the seeds of *Anadenanthera* spp., used in the preparation of a psychotropic snuff, caught the attention of the Hungarian biochemist Stephen Szára who conducted a series of experiments with the drug in humans. Many other studies with the pure compound followed and its powerful visionary effects were highlighted. As will become evident from the data presented in this introduction, DMT appears to fit the characteristics of the so-called psychedelic or hallucinogenic drugs, which according to Hollister (1968) share the following characteristics regarding their human pharmacology: 1) modifications in thought processes, perception and mood predominate over other alterations; 2) intellectual capacity and memory is minimally affected; 3) stupor, narcosis or excessive stimulation are not the predominant effects; 4) autonomic side effects are moderate; 5) addictive craving is minimal. The classification of DMT into this pharmacological group is further supported by its chemical structure, and its receptor affinity profile, since according to Glennon, the "classical hallucinogens" are "agents that meet Hollister's original definition, but also: a) bind at 5-HT_2 serotonin receptors, and b) are recognized by animals trained to discriminate 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane (DOM) from vehicle" (Glennon, 1999), two additional criteria which DMT has been demonstrated to meet.

3.1. Subjective effects

The first study published in the scientific literature on the subjective effects induced by DMT was reported by Szára, who conducted a series of experiments to investigate whether this tryptamine had a "psychotic effect" in humans (Szára, 1956). After observing that the drug was not orally active in doses as high as 150 mg (2 mg/kg), he and other members of his team self-administered DMT intramuscularly and found it to elicit psychotropic effects from 30 mg (0.2 mg/kg) onwards, the highest tested dose being 150 mg (2 mg/kg; Szára, 1957). The effects described at what the author considered the optimal dose (0.7-1.1 mg/kg) involved visual illusions, disturbances of thought and euphoria, accompanied by tingling sensations, tremors, mydriasis and elevations of blood pressure and pulse rate. The author regarded these effects as qualitatively similar to those elicited by mescaline and lysergic acid diethylamide (LSD), but with a characteristic time course. Indeed, the most striking aspect of DMT was the onset and duration of the "model psychosis": effects were first felt around 3-5 min following i.m. injection and had disappeared after 1 h. Szára (1957) gave the following account of the effects he had experienced when he first self-administered 75 mg i.m. of DMT:

> In the third or fourth minute after the injection vegetative symptoms appeared such as tingling sensation, trembling, slight nausea, mydriasis, elevation of the blood pressure and increase of the pulse rate. At the same time eidetic phenomena, optical illusions, pseudo-hallucinations, and later real hallucinations, appeared. The hallucinations consisted of moving, brilliantly colored oriental motifs, and later I saw wonderful scenes altering very rapidly. The faces of the people seemed to be masks. My emotional state was elevated sometimes to euphoria. At the highest point I had compulsive athetoid movement in my left hand. My consciousness was completely filled by hallucinations, and my attention was firmly bound to them; therefore I could not give an account of the events happening around me. After ¾ - 1 hour the symptoms disappeared and I was able to describe what had happened.

In a subsequent paper, Sai-Halász et al. (1958) summarized the main subjective effects elicited by i.m. DMT (0.7-1.0 mg/kg) in a group of 30 healthy volunteers, mainly medical doctors, as follows: 1) perceptual modifications which were mainly visual, rapidly changing colorful illusions and hallucinations; 2) modifications of spatial perception, with changes in

room dimensions; 3) modifications of bodily image, with subjects reporting that parts of their body no longer belonged to them; 4) modifications of time perception, with volunteers usually overestimating the duration of effects; 5) thought modifications with loosening of associations, incoherence of speech and difficulties to control their trains of thoughts. In some cases suspiciousness and paranoid ideation were observed; 6) affective modifications consisting mainly of euphoria or uncontrollable laughter. Fear was also common, mainly during the first minutes of intoxication; 7) in some cases, clouding of consciousness was observed, with volunteers being unable to recall events for several minutes.

The above observations were confirmed in general terms by Arnold and Hofmann (1957) in Germany employing i.m. doses of 1.0-1.2 mg/kg and replicated in other papers by the Hungarian group (Sai-Halász, 1962) who tested doses in the 0.35-0.83 mg/kg range, also by the i.m. route. It is interesting to note that while the subjective effects of this new "psychoticum", as the Hungarian research team had a priori labeled DMT (Sai-Halász et al., 1958), were quite reproducible in their group of normal volunteers, the researchers noted that the DMT experience did not definitively resemble schizophrenia or other endogenous psychoses. This led them to conduct drug-administration experiments with chronic schizophrenics. In these patients, 1-1.5 mg/kg i.m. doses of DMT induced feelings of strangeness, mood changes and autonomic effects but the visual images which characterized the experiences of healthy subjects were virtually absent (Böszörmenyi and Szára, 1958).

In the United States, initial research on the human pharmacology of DMT was conducted by Turner and Merlis (1959) in schizophrenic patients, first testing the drug intranasally (5-20 mg, i.e., 0.07-0.27 mg/kg) and orally (doses up to 350 mg, i.e., 4.7 mg/kg) and finding it to be inactive by these routes. These investigators only observed "unilateral flushing of the face and mydriasis" in one patient who had received 10 mg intranasally. In contrast, intravenous (5-25 mg, i.e., 0.07-0.33 mg/kg) and intramuscular (5-50 mg, i.e., 0.07-0.67 mg/kg) doses of the drug induced states of anxiety, restlessness, and a very intense dysphoric reaction in one patient (Turner and Merlis, 1959). At the Addiction Research Center in Lexington, Kentucky, results obtained by Rosenberg and coworkers (1963) in convicted former opiate addicts who "volunteered" for a DMT study, highlighted visual distortions and hallucinations, among other drug effects on the psychological sphere, after the administration of 0.75-1.0 mg/kg i.m. In a later cross-tolerance experiment in which LSD and DMT (0.5-1.0 mg/kg i.m.) were administered, these researchers found these two drugs to differ only in the time course of the

intoxication and concluded that they elicited similar autonomic and subjective effects. The latter included "euphoria, anxiety, visual hallucinations and perceptual distortions" (Rosenberg et al., 1964).

Subsequent studies conducted with non-psychotic subjects also stressed the predominance of visual phenomena during the intoxication (Gillin et al., 1976). However, these appear to be only part of the overall psychological experience. Bickel and coworkers (1976) found that DMT could be differentiated from placebo at low 0.25 mg/kg i.m. doses by means of self-report scales measuring (from highest to lowest scores): derealization, visual phenomena and altered body image. The lowest scores, although statistically significant, were obtained for scales measuring dysphoria, euphoria and delusion. The DMT syndrome was also characterized by somatic effects which included altered equilibrium, numbness in hands and feet, heaviness of the legs and dizziness. In a comparative study with 0.25 mg oral THC and placebo (Dittrich et al., 1976), 0.25 mg/kg i.m. DMT induced increases in scales measuring thought modifications, visual illusions and body image modification scales. Interestingly, at the administered doses, DMT could not be differentiated from THC. But again, the only aspect which predominated in the DMT-induced state relative to THC effects were the visual illusions which showed higher scores but with only a tendency towards statistical significance.

Strassman and coworkers administered doses from 0.05 to 0.4 mg/kg intravenously to healthy experienced psychedelic drug users (Strassman and Qualls, 1994; Strassman et al., 1994; Strassman et al., 1996). At the higher dose, drug effects were characterized by an intense "rush" which was followed by colorful hallucinations, very intense emotional effects and perceptual modifications conferring an oneiric quality to the experience. This modified state of awareness was described as being very compelling, totally replacing the previously ongoing mental activity. At 20-30 min following administration, when plasma levels decreased to levels slightly above the limit of detection, the subjective effects reported had completely disappeared. In one of these studies (Strassman et al., 1994), the authors obtained interesting dose-response data regarding subjective effects. At the lower 0.05 and 0.1 mg/kg doses, emotional and somatic effects appeared to predominate over perceptual modifications, whereas at the higher 0.2 and 0.4 mg/kg doses drug-induced visual effects and detachment from external reality were described by the volunteers as being overwhelming. In line with previous studies (see for example Sai-Halász et al., 1958), during the initial rush most

volunteers experienced anxiety and opposed emotions like fear and euphoria coexisted throughout the intoxication in some cases.

In summary, in the clinical studies reviewed, DMT was found to be psychologically inactive by the oral and intranasal routes in doses up to 4.7 mg/kg and 0.27 mg/kg, respectively. Distinct psychotropic effects were observed, however, when the drug was administered by the i.m. route, commonly in doses around 0.7-1 mg/kg, with the maximal reported dose being 2 mg/kg. The i.v. route has also proved to be effective, with a maximal reported dose of 0.4 mg/kg and the threshold dose for psychedelic effects around 0.2 mg/kg.

3.2. Pharmacokinetics

In the course of the first trials in which pure DMT was administered to humans, it soon became apparent that DMT was devoid of psychoactive effects after oral administration (Szára, 1957). This peculiarity was later corroborated by Turner and Merlis (1959), who extended the observation to intranasally administered DMT. The drug thus appears to be the only psychedelic known to be psychologically inactive per os, although this has also been postulated for 5-methoxy-DMT and contested in a recent paper (Ott, 2001). The lack of oral activity for DMT led early researchers to administer the drug parenterally, and the scarce human data available on the pharmacokinetics of DMT have been obtained after its i.m and i.v. administration. It is also interesting to note that despite the several papers indicating that DMT does not exert psychoactive effects in oral doses of several hundred milligrams (Szára, 1957; Turner and Merlis, 1959), no study has been conducted to date to assess the metabolic fate of DMT following its oral administration. Thus, the metabolic pathways involved in what appears to be an extensive first pass effect have not been established in humans and the data available on the in vivo degradation of DMT have been obtained after its parenteral administration, mainly in animals.

In his first paper on DMT, Szára (1956) identified 3-indoleacetic acid (IAA) in urine as a metabolite of the drug following its i.m. administration in doses of 0.7–1.1 mg/kg. The amounts recovered ranged from 8 to 25% of the administered dose and no unmetabolized DMT was found in the samples. The authors postulated that the rapid metabolism of DMT could explain the short duration of the drug-induced “psychosis”. In this paper, no data were given regarding plasma levels of the metabolite or the parent compound.

Kaplan and coworkers (1974) found mean peak concentrations of 100 ng/ml at 10-15 min following an i.m. injection of 0.7 mg/kg to eleven male subjects. The drug also disappeared from plasma very rapidly. By 1h, DMT had almost disappeared and the concentration vs. time figure showed that virtually no DMT could be quantified at 2 h. Subjective effects appeared to closely parallel DMT plasma levels. Both the subjective "high" and the maximum drug concentration in plasma were found at 10 min and both returned to baseline levels around 1 h. These researchers pointed out the large individual variability in peak plasma concentration, which oscillated approximately between 20 and 150 ng/ml, and the apparent similar time course between individuals. Drug levels in 24 h urine showed only an average of 0.069% of the administered dose was recovered in urine, most of which was excreted within the first 2 h. They consequently argued that the drug was rapidly metabolized, but no study was conducted in order to identify the putative metabolites.

Strassman and Qualls (1994) measured DMT plasma levels between 2 and 60 min following an i.v. bolus of 0.05, 0.1, 0.2 and 0.4 mg/kg doses. Drug effects were found to initiate almost instantaneously. DMT plasma levels could be measured up to 30 min after injection and had virtually disappeared at 60 min for all doses. Mean peak value at 2 min after the 0.4 mg/kg dose was approximately 90 ng/ml and showed marked interindividual variability, with a range of 32-204 ng/ml. As in the studies discussed above, pharmacokinetic parameters were not reported and the authors only stated that "generally, a doubling of dose resulted in a doubling of Δmax values". Neither were DMT metabolites assessed.

3.3. Cardiovascular effects

Early studies on DMT repeatedly described increases in blood pressure following drug administration to humans, both in uncontrolled (Szára, 1956; Böszörmenyi and Szára, 1958; Sai-Halász et al., 1958) and also in placebo-controlled studies in which 1 mg/kg i.m. doses were administered (Rosenberg et al., 1963; Rosenberg et al., 1964). Heart rate has been found to increase in relation to pre-drug values, although less markedly than blood pressure, in non-placebo-controlled studies enrolling healthy volunteers (Sai-Halász et al., 1958) and psychiatric patients (Böszörmenyi and Szára, 1958). However, other authors have failed to observe statistically significant increases for this variable compared with placebo (Rosenberg et al., 1963; Rosenberg et al., 1964). In a more recent study, Strassman and Qualls (1994)

reported dose-dependent statistically significant increases in mean arterial blood pressure and heart rate after 0.2 and 0.4 mg/kg doses of i.v. DMT.

3.4. Autonomic effects

Increases in pupil diameter were observed in early non-placebo-controlled studies with DMT, after its i.m. administration to both healthy volunteers in doses of 0.7-1.0 mg/kg (Sai-Halász et al., 1958) and to chronic schizophrenics in doses of 1.0-1.5 mg/kg i.m. (Böszörmenyi and Szára, 1958). Gillin and coworkers (1976) also described mydriasis after the i.m administration of a 0.7 mg/kg dose in an uncontrolled study. DMT-induced mydriasis after a 1 mg/kg i.m. dose was confirmed in placebo-controlled studies by Rosenberg and coworkers (1963), who replicated these findings in a subsequent study (Rosenberg et al., 1964) with the same dose. More recently, the same effect has been observed by Strassman and Qualls (1994), who found statistically significant increases in pupil diameter after 0.4 mg/kg i.v. DMT in double-blind placebo-controlled conditions.

Strassman and Qualls (1994) also measured the effects of DMT on rectal temperature and found increases after the higher 0.2 and 0.4 mg/kg doses. However, these results were not replicated in a subsequent study by these authors in which repeated 0.3 mg i.v. DMT doses were administered at 30 min intervals. The authors argued that the slow increase in this variable and the short interval between doses may have precluded significant elevations after the first DMT injection (Strassman et al., 1996).

3.5. Neuroendocrine effects

DMT increases serum levels of prolactin, growth hormone and cortisol in humans (Meltzer et al., 1982). These authors found that the administration of a 0.7 mg/kg i.m. dose produced increases in prolactin and cortisol beginning as early as 10 min after injection and peaking at 30 min. This was in contrast with growth hormone, which began to rise at 60 min. No effect of DMT on follicle stimulating hormone, thyroid stimulating hormone or luteinizing hormone secretion was observed. Pretreatment with the serotonin antagonist cyproheptadine only inconsistently inhibited the rise in cortisol and prolactin but effectively blocked the increase in growth hormone in all three subjects participating in the study. In a subsequent single-

subject experiment, pretreatment with haloperidol increased both the subjective effects of DMT and the rise in growth hormone.

Strassman and Qualls (1994) found DMT to dose-dependently increase blood levels of corticotropin, β-endorphin and prolactin after i.v. administration of doses between 0.05 and 0.4 mg/kg. Statistically significant increases were obtained after the higher 0.2 and 0.4 mg/kg doses. Peak levels for these hormones were found between 5 and 10 min after injection. Cortisol levels were also significantly raised but increases peaked later, at 15-30 min. No drug effects were seen for growth hormone or melatonin levels. In a subsequent study, Strassman et al. (1996) replicated and expanded their previous results, reporting significant increases for prolactin, cortisol and adrenocorticotropic hormone after an i.v. dose of 0.3 mg/kg.

3.6. Adverse effects

Under the Substance-Related Disorders, the Diagnostic and Statistical Manual of Mental Disorders in its 4th edition (American Psychiatric Association, 1994) lists the following hallucinogen-related disorders:

A) Hallucinogen use disorders, which include hallucinogen abuse and dependence.
B) Hallucinogen-induced disorders:
    1. Hallucinogen-Induced Anxiety Disorder
    2. Hallucinogen-Induced Mood Disorder
    3. Hallucinogen Persisting Perception Disorder (Flashbacks)
    4. Hallucinogen-Induced Psychotic Disorder, with Delusions
    5. Hallucinogen-Induced Psychotic Disorder, with Hallucinations
    6. Hallucinogen Intoxication Delirium
    7. Hallucinogen-Related Disorder Not Otherwise Specified

While repeated use of certain psychedelics, such as LSD, has been described to lead to tolerance to the psychological effects, abstinence symptomatology has not been described. The most frequently described acute adverse event in the course of psychedelic drug intoxication is the occurrence of an intense panic state commonly known as a “bad trip”. These events have been described to respond to verbal reassurance and to treatment with benzodiazepines (Strassman, 1984). At the subacute level, the occurrence of the intriguing

and controversial Hallucinogen Persisting Perception Disorder has been recently reviewed by Halpern and Pope (2003). In this work the authors conclude that the disorder "appears to be a genuine but uncommon disorder, sometimes persisting for months or years after hallucinogen use and causing substantial morbidity". Another aspect of psychedelic drug use that has been the object of controversy is whether the repeated exposure to these compounds leads to neuropsychological toxicity. This has also been reviewed by Halpern and Pope (1999) with inconclusive results. However, the authors indicate that "there are few, if any, long-term neuropsychological deficits attributable to hallucinogen use."

In the specific case of DMT, virtually all early DMT studies described episodes of anxiety and dysphoria after acute administration of the drug (see the Subjective Effects section above). More recently, Strassman also reported the occurrence of anxiety after i.v. DMT administration (Strassman et al., 1994) and commented on the potentially traumatic nature of high-dose hallucinogen sessions (Strassman, 1995). This author reported an incidence of flashbacks in 5-10% of his study participants who had received at least one high 0.4 mg/kg DMT dose (Strassman, 1995), and the withdrawal of one volunteer due to the development of a depression in the course of the study (Strassman, 1994).

4. Mechanism of action of DMT and related compounds

4.1. Receptor level interactions

Psychedelic phenylalkylamines and indolealkylamines show remarkable structural similarities with serotonin, norepinephrine and dopamine, the main endogenous neurotransmitter amines, and through the years, interaction with each of these neurotransmitter systems has been proposed as the mechanism of action of these drugs. However, while few data support a direct action of psychedelics on noradrenergic and dopaminergic neurotransmission, biochemical and behavioral data suggest the targeting of serotonergic receptors as a common feature of the classical psychedelics. Among serotonergic receptors, the candidate most likely to mediate psychedelic drug effects is the 5-HT_{2A}, as will be discussed below. Other receptor subtypes believed to be targeted by these drugs are the 5-HT_{2C}, which shows a high degree of homology with the 5-HT_{2A} site, and the 5-HT_{1A}, the latter showing high affinity for indolealkylamines, but not for phenylalkylamines. All three subtypes are G-protein-coupled receptors consisting of seven transmembrane helices connected by intracellular and

extracellular loops. While the 5-HT_{2A} and 5-HT_{2C} are positively coupled to phosphoinositide hydrolysis, the 5-HT_{1A} subtype is negatively coupled to adenylate cyclase. 5-HT_{2A} receptors show the highest densities in the neocortex, while 5-HT_{2C} receptors predominate in the choroid plexus and 5-HT_{1A} are mainly found in the hyppocampus, amygdala, limbic cortex and notoriously in the raphe nuclei where they act as somatodendritic autoreceptors (for a review see Glennon and Dukat, 1995).

Initial studies on LSD–serotonin interactions in peripheral tissue found that LSD antagonized smooth muscle contraction induced by serotonin (Gaddum, 1953) and serotonin antagonism was consequently proposed as the mechanism underlying psychedelic effects (Woolley and Shaw, 1954). In subsequent experiments, LSD was also found to display agonist activity in other systems and this was put forward as an alternative hypothesis explaining its psychotropic properties (Shaw and Woolley, 1956). Substantial information on the mechanism of action of these compounds was obtained later from research in behaving animals by means of various models, most prominently the drug discrimination paradigm. In these studies, rodents are trained to discriminate between a known psychedelic such as LSD, 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI) or DOM and saline, and subsequently, the percentage of substitution elicited by the drug under investigation is assessed. Early work employing this paradigm evidenced that the stimulus effects of the phenylalkylamine compounds such as DOM generalized to other structurally related phenylalkylamines, but also to indolealkylamines such as LSD and a large number of methylated tryptamines, including DMT (Glennon et al., 1983b). Alternatively, when the indolealkylamines LSD or 5-MeO-DMT were used as the training stimulus, adequate responding generalized to DOM, mescaline and many other phenylalkylamines (Glennon et al., 1993a). These results suggested a common mechanism of action underlying the interoceptive effects of both structural groups. It was also found that the serotonergic 5-HT_2 antagonists such as ketanserin and pirenperone blocked the discriminative stimulus effects of DOM and its generalization to LSD, 5-MeO-DMT and mescaline (Glennon et al., 1983c). Based on these results, it was proposed that the psychedelics act as agonists at 5-HT_2 receptors (Glennon et al., 1983c). In the specific case of DMT, complete stimulus generalization (greater than 80% appropriate responding) has been shown to occur in rats trained with LSD, 5-MeO-DMT and DOM (Glennon et al., 1983a), suggesting a common mechanism of action with these drugs. A more recent study has found a somewhat lower level

of substitution (77.9%) in rats trained with LSD as a discriminative stimulus (Helsley et al., 1998a).

Subsequent radioligand binding studies in animals examined the binding of various psychedelics at different populations of serotonin receptors and common sites could be identified for the two main structural families. Thus, in vitro autoradiography revealed high affinity binding sites for ^{125}I-DOI (McKenna et al., 1987) in regions previously shown to contain high densities of 5-HT_2 receptors as measured by means of ^{125}I-LSD autoradiography (Nakada et al., 1984). In a subsequent study, McKenna and Saavedra (1987) showed that LSD and 1-(2,5-dimethoxy-4-bromophenyl)-2-aminopropane (DOB) cross-displaced ^{125}I-DOI and ^{125}I-LSD in specific rat brain regions, and the authors speculated that psychedelic drug effects might be mediated by receptors common to the ergolines and the phenylalkylamines. More detailed in vitro receptor binding studies showed differential affinity for the 5-HT_2 and the 5-HT_{1A} sites between phenylalkylamine and indolalkylamine compounds. While LSD and DMT displayed nanomolar affinity for both 5-HT_{1A} and 5-HT_2 receptors, the phenylalkylamines DOB, DOM, DOI and many others were selective for the 5-HT_2 (McKenna et al., 1990; Pierce and Peroutka, 1989; Titeler et al., 1988). In the study by Pierce and Peroutka (1989), the affinity of LSD, DMT, DOB and DOI for non-serotonin receptors was also assessed. While all four displayed virtually no affinity for benzodiazepine binding sites tested, the phenylalkylamines showed micromolar affinity for the muscarinic, α_1-, α_2- and β-adrenergic receptors. LSD also bound to the adrenergic receptors, displaying high (nanomolar) affinity for the α_2-adrenergic receptor. Finally, DMT displayed micromolar affinity for the α_1- and α_2-adrenergic receptor, and no interaction with the β-adrenergic, muscarinic and benzodiazepine receptor sites. Thus, despite particular interactions with other receptors which may modulate the overall effects, affinity for the 5-HT_2 site appears to be a common feature of compounds with a disparity of chemical structures but able to induce psychedelic effects in humans. Glennon and coworkers (1984) found a high correlation between psychedelic potency in humans and 5-HT_2 binding affinity, and also between ED_{50} values from drug discrimination studies and 5-HT_2 binding affinity. Thus, the 5-HT_2 receptor was singled out as a likely candidate for the site of action of psychedelic drugs.

Other serotonin receptor subpopulations such as the 5-HT_{1A} have been implicated in the mechanism of action of these drugs. As mentioned above, contrary to phenylalkylamines,

indolealkylamines display high affinity for the 5-HT_{1A} receptor (Pierce and Peroutka 1989; Titeler et al., 1988). This led researchers to investigate to which extent this receptor participates in their pharmacology. Two different studies have respectively either failed to find (Glennon et al., 1984) or observed (Titeler et al., 1988) a significant correlation between potency in humans or ED_{50} in animals and binding affinity for the 5-HT_{1A} receptor. However, the fact that DOM-stimulus generalization does not occur for 5-HT_{1A} agonists (Glennon et al., 1986), led Titeler and coworkers (1988) to conclude that 5-HT_{1A} agonism "may not play a primary role in the mechanism of action of hallucinogenic agents". More recently, Strassman (1996) reported that pretreatment with the 5-HT_{1A} antagonist pindolol enhanced, rather than decreased, the subjective effects of i.v. DMT in humans.

To make things more complicated, psychedelic phenylalkylamines and indolealkylamines have also been found to bind to the 5-HT_{2C} (formerly labeled 5-HT_{1C}) receptor, identified by Pazos and coworkers (Pazos et al., 1984). Psychedelic compounds such as DOI and DOM, used as training drugs in the drug discrimination paradigm, and which had been previously considered to bind selectively to the 5-HT_{2A} receptors, were also found to interact with the 5-HT_{2C} receptor (Glennon et al., 1992; Sanders-Bush, 1994). It was thus postulated that many actions initially attributed to the 5-HT_{2A} might have in fact been mediated by the 5-HT_{2C} receptor or a combination of 5-HT_{2A} and 5-HT_{2C} mechanisms (Glennon et al., 1992). However, more recent work has found that the 5-HT_{2A} receptor rather than the 5-HT_{2C} receptor mediates the stimulus effects of LSD (Fiorella et al., 1995). Similarly, Schreiber et al. (1994) and Smith et al. (1999) found that the discriminative stimulus effects of DOI are blocked by the selective 5-HT_{2A} antagonist MDL 100,907, but not by the selective 5-HT_{2C} antagonist SB 200,646. Furthermore, Smith et al. (1999) found an association between the behavioral tolerance to the effects of DOI and the down-regulation of the 5-HT_{2A} but not of the 5-HT_{2C} receptors. Table 6 shows DMT affinity values at various receptors.

Table 6: DMT radioligand binding data at serotonergic, benzodiazepine, muscarinic cholinergic, opioid and adrenergic receptors.

	K_i (nM)									
	5-HT$_{2A}$	**5-HT$_{2C}$**	**5-HT$_{1A}$**	**5-HT$_{2B}$**	**BZD**	**Musc.**	**Opioid**	**α_1**	**α_2**	**β**
Glennon et al., 2000[a]	323/ 660	1450	200	-	-	-	-	-	-	
Deliganis et al., 1991[b]	440/ 455	-	130/ 464	-	-	-	-	-	-	-
Sadzot et al., 1989[c]	462/ 1200	-	-	-	-	-	-	-	-	-
Lyon et al., 1988[d]	1200/ 64	-	-	-	-	-	-	-	-	-
	IC_{50} (nM)									
McKenna et al., 1990[e]	75	-	170	450	-	-	-	-	-	-
Pierce and Peroutka, 1989[f]	12	-	170	-	>100,000	88,000	-	4,400	1,200	>100,000

BZD=benzodiazepine, Musc.=muscarinic cholinergic, α_1=α_1-adrenergic, α_2=α_2-adrenergic, β=β-adrenergic. (-) = not determined.

[a] Radioligands: [^{3}H]DOB/[^{3}H]Ketanserin (5-HT$_{2A}$), [^{3}H]8-OH DPAT (5-HT$_{1A}$), [^{3}H]Mesulergine (5-HT$_{2C}$), [^{3}H]N-methylspiperone (D_2), [^{3}H]RO15,1788 (BZD).

[b] Radioligand: [^{3}H]Ketanserin (5-HT$_2$), [^{3}H]8-OH DPAT (5-HT$_{1A}$). Two values reported at each site corresponding to absence / presence of 10^{-4} M GTP.

[c] Radioligand: [^{3}H]Ketanserin (5-HT$_2$). Two values reported corresponding to human cortex / rat cortex, respectively.

[d] Radioligands: [^{3}H]Ketanserin / [^{3}H]DOB. Two values reported corresponding to: [^{3}H]Ketanserin / [^{3}H]DOB, respectively.

[e] Radioligands: [^{3}H]8-OH DPAT (5-HT$_{1A}$) [^{125}I]-R-(-)DOI (5-HT$_{2A}$), [^{3}H]Ketanserin (5-HT$_{2B}$).

[f] Radioligands: [^{77}Br]-R(-)DOB (5-HT$_{2A}$), [^{3}H]8-OH DPAT (5-HT$_{1A}$), [^{3}H]Flunitrazepam (BZD), [^{3}H]Quinuclidinylbenzylate (QNB, Muscarine Cholinergic), [^{3}H] WB-4101 (α_1-adrenoceptor), [^{3}H] Rauwolscine (α_2-adrenoceptor), [^{3}H] DHA (β-adrenoceptor).

Despite the evidence derived from animal studies, the nature of the interaction of psychedelics at the 5-HT$_{2A}$ sites has been the object of controversy regarding whether these drugs act as agonists or antagonists. As mentioned above, results from discriminative stimulus antagonism tests indicated that drug interoceptive effects are primarily mediated via an agonistic action at 5-HT$_{2A}$ receptors. Pierce and Peroutka (1988), however, challenged this concept based on results from second messenger studies. The 5-HT$_{2A}$ receptor is coupled to stimulation of phospholipase C through activation of a G-protein. Receptor stimulation results in the hydrolysis of phosphatidylinositol 4,5-biphosphate by phospholipase C and the generation of inositol 1,4,5-triphosphate and diacylglycerol. In turn, inositol triphosphate and diacylglycerol lead to a series of intracellular events, most prominently the activation of protein kinases (Sanders-Bush and Canton, 1995). Pierce and Peroutka (1988) found LSD to antagonize the

maximum effects of serotonin on phosphoinositide hydrolisis and proposed that LSD acts as a 5-HT_2 antagonist. In the case of DMT, a series of studies on drug-induced phosphoinositide hydrolysis led to seemingly contradictory profiles of activity, the drug being characterized either as a full agonist (Smith et al., 1998), a partial agonist (Cory et al., 1987; Rabin et al., 2002) or an antagonist (Deliganis et al., 1991). In this model, DMT has consistently been shown to elicit a maximum effect (intrinsic efficacy) below that of serotonin, the full agonist. Nevertheless, in all four studies, DMT increased phosphoinositide hydrolysis above baseline levels, which would argue for agonistic activity. Cory et al. (1987), Rabin et al. (2002) and Deliganis et al. (1991) all found for DMT an intrinsic efficacy which was 20% that of serotonin, i.e., the drug displayed partial agonist activity. Nevertheless, while the former two authors characterized the drug as a partial agonist, in the study by Deliganis et al. (1991), the fact that increasing doses of DMT decreased the maximum effect exerted by a fixed serotonin concentration -as would be expected from a partial agonist- was erroneously interpreted as an antagonistic effect of DMT. At the other end of the spectrum, Smith et al. (1998) found for DMT an intrinsic efficacy of 90% that of serotonin, which led the authors to characterize the drug as a full agonist. Thus, the largest discrepancy between these studies is the intrinsic efficacy of the drug, but all four indicate that DMT mimics the stimulatory effect of serotonin in phosphoinositide hydrolysis, suggesting partial agonist activity. Partial agonist activity has also been demonstrated for LSD, DOI, 5-MeO-DMT and mescaline in human neuroblastoma cells transfected with the 5-HT_2 receptor (Newton et al., 1996); for LSD DOI and DOM in rat cerebral cortex (Edwards et al., 1992; Sanders-Bush et al., 1988); for 5-MeO-DMT and bufotenine in rat tumoral cells (Cory et al., 1987); and for LSD, bufotenine, DOM, 5-MeO-DMT, DOI, and DOB in recombinant cells expressing 5-HT_2 receptors (Egan et al., 2000).

Further support for the 5-HT_{2A} (partial) agonism hypothesis arises from the fact that repeated exposure to indolealkylamine (LSD) and phenylalkylamine (DOI, DOB, DOM) psychedelics provokes a selective down-regulation of 5-HT_{2A} receptors (Aloyo et al., 2001; Anji et al., 2000; Buckoltz et al., 1985; Buckholtz et al., 1988; Buckholtz et al., 1990; Leysen et al., 1989; McKenna et al., 1989; Smith et al., 1999), a phenomenon that can be related to the development of tolerance to the behavioral effects of these drugs (Leysen et al., 1989; Smith et al., 1999). In contrast, it has been observed that repeated administration of LSD and DOM does not affect binding to 5-HT_{1A}, 5-HT_{1B}, β-adrenergic, α_1- or α_2-adrenergic or D_2-dopaminergic or to the serotonin transporter, suggesting that tolerance is not mediated by drug actions at these receptors (Buckholtz et al., 1990; Leysen et al., 1989).

Glennon (1990) reexamined the agonism-antagonism controversy and concluded that hallucinogens are not 5-HT_2 antagonists, but agonists, or at least partial agonists, at 5-HT_2 receptors. This author argued that some of these compounds display a low intrinsic activity; and may thus appear to antagonize the maximum effect of the full agonist (serotonin) when tested in combination.

4.2. DMT as a monoamine oxidase inhibitor (MAOI)

Monoamine oxidases A and B are flavoproteins located in the outer mitochondrial membrane. They catalyze the oxidation of amines to aldehydes. These enzymes oxidize endogenous neurotransmitters and also xenobiotics. MAO-A preferentially oxidizes norepinephrine and serotonin and is selectively inhibited by clorgyline. MAO-B preferentially degrades phenylethylamine and is selectively inhibited by *l*-deprenyl. The neurotransmitter dopamine is oxidized by isoforms A and B. Both forms are present in the human brain and peripheral organs, with high levels found in the liver (Saura et al., 1996). DMT is a substrate of MAO (Suzuki et al., 1981) and there is evidence that the drug displays MAO-inhibitory activity to some extent. Ho et al. (1970) examined a series of substituted dimethylaminoethylindoles and dimethylaminomethylindoles (gramines) and found for DMT an IC_{50} value in the millimolar range. This is, however, significantly less active than the β-carbolines, which have IC_{50} values between the micromolar and the 100 nanomolar range (see section 7.2. below). In the study by Ho et al. (1970), DMT was the most active in the dimethylaminoethylindole series followed in order of decreasing potency by 5-methyl-DMT > 5-MeO-DMT > 5-hydroxyl-DMT. Barlow (1961) found that millimolar concentrations of DMT inhibited tyramine oxidation by 80% and tryptamine oxidation by 44% in suspensions of guinea pig liver. Furthermore, DMT appeared to inhibit serotonin oxidation more potently, with 100 μM concentrations reducing MAO activity between 50 and 90%. These results indicate that DMT acts as a weak MAO inhibitor and suggest that it has a higher affinity for MAO-A than for MAO-B. A more recent study has found that, at low concentrations, DMT has affinity for both types of MAO, while at high concentrations the drug binds preferentially to isoform B (Suzuki et al., 1981).

4.3. Electrophysiological effects

The ability of the classical psychedelics to temporarily modify perception, cognition and mood has been interpreted as indicating a direct drug action on the neocortex or an indirect action on subcortical structures projecting to the neocortex (Marek and Aghajanian, 1998a). Early studies on the effects of psychedelics on neuronal electrical activity found LSD to potently and reversibly inhibit the tonic firing of serotonergic neurons in the dorsal raphe nucleus (Aghajanian et al., 1968), a subcortical structure located in the brainstem. This notion was later extended to other indolealkylamines such as DMT, 5-MeO-DMT and psilocin (Aghajanian and Haigler, 1975; Aghajanian et al., 1970; Rogawsky and Aghajanian, 1981), but was found to be inconsistent for the phenylalkylamines (Aghajanian et al., 1970; Haigler and Aghajanian, 1973). This ability to "antagonize" serotonergic neurotransmission was later found to be dependent on the interaction of these drugs at the 5-HT_{1A} somatodendritic autoreceptor (Aghajanian, 1995), of which serotonergic raphe neurons show a high density. At this level, indolealkylamines mimicked, rather than antagonized, serotonin. However, raphe neurons decreased their firing rate due to the autoreceptor-mediated inhibition. As discussed in the previous section, indolalkylamines demonstrate similar affinity for the 5-HT_{1A} and 5-HT_{2A} sites, whereas phenylalkylamines are fairly selective for the latter. It thus became evident that activity at the 5-HT_{1A} receptor level is not a common feature of the two main structural groups of psychedelic agents. Furthermore, the fact that not all drugs displaying agonist of partial agonist activity, e.g., buspirone, show psychedelic properties, together with the lack of a consistent correlation between affinity at this site and human psychedelic potency led researchers to the conclusion that inhibition of serotonergic neurotransmission must not be the underlying mechanism of psychedelic drug activity (Aghajanian, 1994).

What all classical psychedelics share is their ability to bind to the 5-HT_2 receptor family, and, as mentioned above, affinity at this level shows a good correlation with drug potency in humans and in drug discrimination animal models. Within the 5-HT_2 class, the 5-HT_{2B} receptor is mainly expressed in peripheral tissue and the 5-HT_{2A} predominates over the 5-HT_{2C} receptor throughout the neocortex (Pompeiano et al., 1994), making the former the most likely candidate for mediating psychedelic drug action. Thus, electrophysiological studies have mainly explored the effects of serotonin and psychedelics on 5-HT_{2A} receptors located in cortical regions.

The main effect of serotonin on cortical 5-HT_{2A} receptors is the induction of postsynaptic potentials, that can be inhibitory or excitatory depending on the brain region studied (Aghajanian and Marek, 1999a). In the rat piriform cortex, a paleocortical brain structure, serotonin evokes inhibitory postsynaptic potentials (IPSPs) in layer II pyramidal cells, through excitation of a subpopulation of GABAergic interneurons located in the border between layers II and III (Sheldon and Aghajanian, 1990; Sheldon and Aghajanian, 1991). This effect is mimicked by DOM, LSD and DOI but with a lower intrinsic efficacy, i.e., these compounds again appear to display partial agonist activity (Marek and Aghajanian, 1996; Marek and Aghajanian, 1998a; Sheldon and Aghajanian, 1990). In addition, the effect is blocked by selective 5-HT_{2A} antagonists (Marek and Aghajanian, 1994). Conversely, in the neocortex, serotonin and DOB interaction with the 5-HT_{2A} receptors lead to increases in membrane excitability of layer V pyramidal neurons (Araneda and Andrade, 1991). In a later study, bath application of serotonin was found to induce, via activation of the 5-HT_{2A} receptor, increases in the amplitude and frequency of spontaneous excitatory postsynaptic potentials (EPSPs) and currents (EPSCs). This effect was observed in layer V neurons of brain slices from transitional and neocortical areas, i.e., cingulate, medial prefrontal and fronto-parietal cortex (Aghajanian and Marek, 1997). Serotonin-induced spontaneous EPSPs/EPSCs were not blocked by GABA antagonists, but by selective 5-HT_2 receptors antagonists, and also by AMPA/kainate antagonists, suggesting the involvement of glutamate release in this effect. Despite the fact that glutamate was being released by presynaptic terminals, EPSCs did not appear to depend on the firing of neighboring neurons. In fact, they were also induced by direct application of serotonin at certain specific locations within the apical dendritic field of layer V pyramidal cells. However, selective group II metabotropic agonists acting on presynaptic inhibitory autoreceptors appeared to suppress the serotonin-induced increase in the frequency of EPSCs (Aghajanian and Marek, 1997). Similarly, μ-opiate receptor agonists also blocked the 5-HT induced EPSCs by means of a presynaptic mechanism (Marek and Aghajanian, 1998b). These findings would indicate that serotonin induces the excitatory effect by acting presynaptically, directly or indirectly, through a 5-HT_{2A}-mediated mechanism inducing focal glutamate release on apical dendrites of layer V pyramidal cells (Marek and Aghajanian, 1998c). In addition, the measured amplitude increases could indicate the participation of a postsynaptic amplification mechanism (Aghajanian and Marek, 1997) that could be mediated by 5-HT_2 receptors located in the apical dendrites of pyramidal cells (Jakab and Goldman-Rakic, 1998). The psychedelic phenylalkylamine DOI has been found to increase the amplitude of electrically evoked EPSPs

and also the frequency of spontaneous EPSCs, but to a lesser extent than 5-HT, suggesting partial agonist activity (Aghajanian and Marek, 1997). However, while DOI and LSD have a low efficacy in inducing spontaneous EPSCs, they have been found to enhance late EPSCs evoked by electrical stimulation of afferent fibers (Aghajanian and Marek, 1999a; Aghajanian and Marek, 1999b; Aghajanian and Marek, 2000). This late component involves a specific mechanism of neurotransmitter release termed asynchronous release, which is not promoted by serotonin. This difference between the endogenous neurotransmitter and the classical psychedelics has been proposed to explain why treatments that elevate endogenous serotonin levels do not elicit psychedelic effects (Aghajanian and Marek, 2000). A very recent study has observed DOI to increase the frequency of spontaneous EPSPs in the medial frontal cortex of mice, and also to induce a characteristic behavioral response in whole animals. Both effects could be effectively suppressed by the selective Group II mGlu presynaptic receptor agonist LY379268 (Klodzinska et al., 2002). In conclusion, the latest research suggests that psychedelic 5-HT_{2A} agonists interact with glutamatergic neurotransmission increasing glutamate release, presumably from thalamic afferents (Marek et al., 2001), without enhancing impulse flow. Also, activation of postsynaptic 5-HT_{2A} receptors probably counteracts dendritic inhibitory mechanisms, increasing the range of stimuli causing neurons to fire (Jakab and Goldman-Rakic, 1998).

4.4. Effects on immediate early gene expression

Immediate early genes are activated by external signals and do not require *de novo* synthesis of proteins. Their induction is fast and transient and they are thought to encode transcription factors which will, in turn, modify the expression of other genes known as target genes. The *c-fos* gene is regarded to link external cellular signals with phenotypic changes in brain cells and there exists evidence for the involvement of the Fos protein in the control of behavior. Neuronal activation leads to expression of *c-fos* and the study of this process is believed to provide an in vivo map of cellular responses to a given stimulus (for a review see Herrera and Robertson, 1996). Recently, LSD and DOI administration to rats has been found to stimulate *c-fos* expression in the rat cortex (Frankel and Cunningham, 2002; Gresch et al., 2002; Scruggs et al., 2000; Zhai et al., 2003). LSD increased the levels of the Fos protein in the medial prefrontal cortex and in the anterior cingulate cortex (Frankel and Cunningham, 2002; Gresch et al., 2002); whereas DOI-induced increases in *c-fos* mRNA and Fos protein were observed throughout the cortex (Zhai et al., 2003) and in the somatosensory cortex (Scruggs

et al., 2000), respectively. The involvement of glutamate release in this effect has been demonstrated by the fact that *c-fos* expression by DOI can be reduced by pretreatment with postsynaptic glutamate AMPA antagonists (Scruggs et al., 2000). Furthermore, pretreatment with the presynaptic receptor mGlu2/3 agonist LY379268 was found to block the DOI-induced increase in *c-fos* mRNA in the prefrontal cortex (Zhai et al., 2003). Scruggs and coworkers (2000) observed that lesions of the thalamic afferents to somatosensory cortex reduced the DOI-induced *c-fos* expression. Additionally, Gresch et al. (2002) showed that the majority of cells expressing Fos did not present 5-HT_{2A} receptors. These results suggest an indirect action of 5-HT_{2A} receptors on cortical pyramidal cells, presumably involving glutamate release from thalamo-cortical afferents.

4.5. Tolerance and cross-tolerance

In a review of a large number of studies conducted to determine whether tolerance developed to psychedelic drug administration (Wyatt et al., 1976), this effect was found to occur for LSD, mescaline, DOM and psilocybin in all human trials conducted. Tolerance was also found to develop for these drugs in the vast majority of animal studies examined. This is in sharp contrast with data from DMT. Gillin and coworkers (1976) reported that preliminary data on 4 normal volunteers who received two daily injections of 0.7 mg/kg DMT i.m. for five days were inconclusive in this respect. No consistent changes were found in autonomic variables, subjective ratings or behavior, although a certain decrease in ratings of subjective "high" was recorded. A more recent study (Strassman et al., 1996) found differential tolerance to develop after a dosing regime involving four doses of 0.3 mg/kg DMT i.v. administered at 30 min intervals. Thus, scoring on subjective rating scales or blood pressure increases did not attenuate, whereas neuroendocrine responses (adrenocorticotropic hormone, prolactin and cortisol) and heart rate decreased from the first to the fourth administered dose. Animal studies similarly indicate that tolerance does not develop easily. Thus, failure to develop tolerance has been observed for behavioral and EEG measures in cats (Gillin et al., 1973), and for DMT-induced disruption of operant behavior in primates (Cole and Pieper, 1973). Unlike these authors, Cooper et al. (1981) observed tolerance to the effects of DMT on unconditioned behavior in mice, and Kovacic and Domino (1976) were able to produce a certain degree of tolerance to operant behavior disruption in rats but only by administering very frequent DMT doses for a prolonged period of time, i.e., every 2 h for 21 days.

Another unsettled aspect of DMT pharmacology is whether it displays cross-tolerance with other serotonergic psychedelics. Cross-tolerance has consistently been found between LSD and mescaline and between LSD and psilocybin, both in animal and human studies (Wyatt et al., 1976), as would be expected from drugs with a common mechanism of action despite their different chemical structures. Although statistically significant decreases in subjective ratings and clinical evaluation scores were found after DMT administration to subjects tolerant to LSD in the only human cross-tolerance study performed to date with DMT, these decreases were regarded as moderate by the researchers. What is more, cross-tolerance to the mydriatic effect of DMT could not be demonstrated in this group of subjects who had developed a robust tolerance to the mydriatic effects of LSD (Rosenberg et al., 1964). In animals, Kovacic and Domino (1976) demonstrated that rats tolerant to LSD displayed cross-tolerance to a 3.2 mg/kg DMT dose, but not after a 10 mg/kg dose. Additionally, rats tolerant to 3.2 mg/kg of DMT displayed cross-tolerance to LSD, but strangely, rats tolerant to 10 mg/kg of DMT only displayed minimal tolerance to LSD and for a brief period of time.

4.6. Effects on sensory and sensorimotor gating

Current research with psychedelics has explored the possibility that drugs displaying agonist activity at the 5-HT_{2A} sites temporally disrupt inhibitory neural mechanisms thought to intervene in the normal filtering of information. This hypothesis is based on the assumption of the existence of brain mechanisms directed at filtering out, under normal conditions, the flow of sensory information reaching consciousness. According to this model, serotonergic psychedelics would interact with brain structures involved in the gating mechanisms, temporarily decreasing their functionality and giving rise to the characteristic perceptual and cognitive effects elicited by these agents (Vollenweider, 1994).

Two neurophysiological measures have been developed to evaluate the functionality of neural gating mechanisms: suppression of the P50 auditory evoked potential (AEP) and prepulse inhibition of the startle reflex (PPI). The P50 AEP is a midlatency potential appearing about 50 ms after the presentation of an auditory stimulus (Picton et al., 1974). The consecutive administration of two identical stimuli, a conditioning and testing stimulus, at a certain interstimulus interval, typically 500 ms, leads to a decrease in the amplitude of the second P50 wave (Adler et al., 1982). The amplitude decrement seen for the testing stimulus is thought to obey active inhibitory mechanisms triggered by the conditioning stimulus

(Freedman et al., 1983). P50 suppression is regarded as a measure of sensory gating, and its neural substrates have been located in the hippocampus, in the mesial temporal lobe (Adler et al., 1998).

The second operational measure, PPI, is based on the inhibitory effect of a weak sensory stimulus (the prepulse) on the motor response caused by a stronger startle reflex-eliciting stimulus. The startle reflex is a brainstem reflex occurring after the presentation of intense and sudden sensory stimuli. Prepulse inhibition is obtained when the startling stimulus is preceded 15-400 ms by the prepulse, and it manifests as a decrease in the intensity of the reflex (Blumenthal, 1999). Typically, in PPI studies the habituation of the startle reflex across the experimental session is also measured. In contrast to P50, PPI is considered a measure of sensorimotor gating, given that the response measured is the motor output to the presented stimulus. While the neural circuit mediating the startle reflex is located in the brainstem, prepulse inhibition is regulated by descending projections from areas in the forebrain (Swerdlow et al., 2001).

Studies in animals have evaluated suppression of the N40 potential in rodents in a paired stimuli paradigm, homologous to that of the human P50. In the only study reported to date on the effects of 5-HT_2 modulation of N40 suppression, an unexpected disruptive effect was found for the 5-$HT_{2A/2C}$ antagonist ketanserin. Conversely, the 5-$HT_{2A/2C}$ agonist DOI increased filtering and was also capable to revert the reductions in filtering caused by ketanserin and amphetamine (Johnson et al., 1998). To my knowledge, no study has been carried out to date on the influence of serotonergic psychedelics/entactogens on the human P50 suppression paradigm.

Braff and Geyer (1980) demonstrated an impairment in habituation of tactile startle in rats after administration of the mixed serotonergic agonist LSD. PPI has also been found to be impaired in rats after the 5-$HT_{2A/2C}$ agonist DOI, an effect which can be prevented by mixed 5-$HT_{2A/2C}$ (Sipes and Geyer, 1994) and selective 5-HT_{2A} antagonists (Padich et al., 1996; Sipes and Geyer, 1995). In a recent article, LSD was found to disrupt PPI in rats, and this effect was prevented only by selective 5-HT_{2A} antagonists. Other antagonists with affinity for the 5-HT_{2C}, 5-$HT_{2B/2C}$, 5-HT_{1A}, and 5-HT_6 did not counteract LSD-induced disruptions (Ouagazzal et al., 2001). In the only human study performed to date involving serotonergic psychedelics, the administration of psilocybin provoked a mild though significant increase of

PPI at a prepulse-to-pulse interval of 100 ms, with no significant effects on habituation (Gouzoulis et al., 1998).

4.7. Effects on regional cerebral blood flow and glucose metabolism

In recent years, nuclear medicine techniques have been incorporated to the in vivo study of psychedelic drugs in humans. Although DMT has not been specifically studied, other drugs with similar receptor affinity profiles have been investigated. A PET investigation utilizing ^{18}F-glucose revealed that the most important metabolic changes after psilocybin administration to humans occur predominantly in the temporomedial, frontomedial, frontolateral and anterior cingulate cortices, where an increase in glucose metabolism is observed (Vollenweider et al., 1997). Metabolic increases in frontomedial regions, and more specifically in the anterior cingulate cortex, have also been observed by another research group after psilocybin in a ^{18}F-glucose PET study (Gouzoulis-Mayfrank et al., 1999a). A previous investigation on regional cerebral blood flow after acute mescaline administration also found an increase in perfusion in the frontal lobes (Hermle et al., 1992). In view of these results, a metabolic "hyperfrontality" has been proposed as the whole-brain mechanism involved in the effects of psychedelics (Gouzoulis-Mayfrank et al., 1999a; Hermle et al., 1992; Vollenweider et al., 1997).

5. DMT metabolism and interactions with other drugs

5.1. DMT metabolism

Data from clinical trials have highlighted the short-lived nature of the subjective effects elicited by DMT, the drug's rapid disappearance from plasma, and the low percentage of the administered dose which can be recovered unmetabolized in urine (Kaplan et al., 1974). Also, in vivo studies in animals have attested a very rapid clearance of DMT from various tissues such as plasma, brain, and liver (Cohen and Vogel, 1972; Mandel et al., 1977; Sitaram et al., 1987b), which considered together with human data is suggestive of an extensive and efficacious metabolism. Unfortunately, as already mentioned in the pharmacokinetics section, only one study has assessed DMT metabolism in humans. Following the i.m. administration of DMT, Szára (1956) identified in urine IAA as the drug's degradation product, with no DMT being detected. This finding was in agreement with a previous study by Ersparmer

(1955), who had found this metabolite in rodent urine, and pointed at oxidative deamination, a reaction catalyzed by MAO, as the process involved in the metabolic breakdown of DMT.

Besides monoamine oxidase-catalized oxidative deamination, in vivo and in vitro studies have also identified *N*-oxidation as an important degradative pathway of DMT, and to a lesser extent *N*-demethylation (Sitaram and McLeod, 1990; Sitaram et al., 1997c). Oxidative deamination was found to be a major route in brain liver and kidney, whereas NADPH-dependent microsomal *N*-oxidation predominated in peripheral tissue and was a minor route in the brain (Sitaram et al., 1997c). According to these authors, *N*-demethylation is a minor degradation route for this compound in all tissues examined (Sitaram and McLeod, 1990). Earlier in vitro studies by Fish et al. (1955b) had already identified DMT-*N*-oxide (DMT-NO) and IAA as the main metabolic products of DMT. They also found NMT to be converted to IAA, but not DMT-NO. These investigators concluded that *N*-oxidation was the main metabolic route in the absence of mitochondrial MAO and that the *N*-oxide compound was not an intermediate to IAA formation by MAO. In order to explore routes other than oxidative deamination, Szára and Axelrod (1959) found that incubation of DMT in rabbit liver microsomal fraction (in vitro experiment) pretreated with the MAO inhibitor iproniazid yielded NMT, DMT-NO, 6-hydroxy-DMT and 6-hydroxy-DMT-NO. In the same paper, the authors reported that the administration of DMT in vivo to rats pretreated with iproniazid yielded NMT, tryptamine, 6-hydroxy-DMT, IAA, 6-hydroxy-IAA, but failed to detect DMT-NO and 6-hydroxy-DMT-NO, which had been found in the in vitro experiment. The presence of hydroxylated metabolites in these experiments and the finding that 6-hydroxy-diethyltryptamine appeared to be more active than diethyltryptamine in animal studies (Szára and Hearst, 1962) led to the speculation that some of the hydroxylated metabolites, specifically 6-hydroxy-DMT, might be responsible for the psychedelic effects of DMT (Szára, 1961; Szára and Hearst, 1962). Nevertheless, this was refuted in a later clinical trial in which DMT and 6-hydroxy-DMT were administered to humans and the latter was found to be inactive (Rosenberg et al., 1963). The relevance of hydroxylation as a metabolic pathway of DMT has received no further attention in the most recent studies and 6-hydroxyderivatives have not been assessed in several experiments on the in vivo and in vitro metabolism of DMT and 5-methoxy-DMT (Sitaram and McLeod, 1990).

Besides the metabolites mentioned above, studies by Barker and coworkers (1980) have detected cyclization derivatives of DMT. These investigators reported IAA, NMT, DMT-NO and 2-methyl-tetrahydro-*β*-carboline (MTHβC) as the main DMT metabolites in rat whole brain homogenates, together with traces of tryptamine and 1,2,3,4-tetrahydro-*β*-carboline. No hydroxylated metabolites were detected and the authors justified this arguing that this reaction takes place in peripheral tissue but not in the brain. They also reported that when DMT was incubated in brain homogenates of rats pretreated with iproniazid, IAA formation was reduced by 83%, but unexpectedly, NMT and DMT-NO formation were also reduced by 90%, and no tetrahydro-*β*-carboline could be measured. Based on these results, the authors pointed out that the enhancement of behavioral effects and increments in DMT half-life in tissue observed after pretreatment with iproniazid in other studies (Kovacic and Domino, 1973, cited in Wang Lu and Domino, 1976; Shah and Hedden, 1978; Wang Lu and Domino, 1976) might also be due to the inhibition of *N*-demethylation and *N*-oxidation rather than to a unique and selective inhibition of MAO. However, these results were not replicated by the group of Sitaram, who showed iproniazid to inhibit the formation of indoleacetaldehyde and IAA from DMT in liver homogenates (Sitaram et al., 1987c) but not the formation of DMT-NO. These authors also found iproniazid to increase the levels of DMT in vivo in rat brain, liver, kidney and blood and those of DMT-NO in rat liver (Sitaram et al., 1987b), and to increase rat urinary excretion of unmetabolized DMT, DMT-NO and NMT (Sitaram et al., 1987a). These results would indicate that after MAO inhibition, DMT metabolism is shifted to other functioning routes. The pharmacological modulation of metabolic pathways independent of MAO has been studied in a series of drug-interaction studies. Wang Lu et al. (1978) observed increases in brain and liver DMT levels after pretreatment with SKF-525A, an inhibitor of the microsomal CYP system, whereas Shah and Hedden (1978) did not. In the study by Wang Lu et al. (1978), chronic phenobarbital administration, a drug which stimulates microsomal CYP activity, reduced brain and liver DMT levels. Also, neuroleptics such as haloperidol and chlorpromazine, respectively, decreased and increased, brain DMT levels. In conclusion, all these studies point out that although oxidative deamination of the side chain by monoamine oxidase appears to be the main metabolic pathway of DMT, the drug can also be degraded by other routes, mainly *N*-oxidation, but possibly also by *N*-demethylation, 6-hydroxylation and cyclization. The extent to which these pathways may be active or even predominate when the drug is administered orally concomitantly with selective MAO inhibitors, as is the case in *ayahuasca* potions, remains to be assessed.

5.2. DMT interactions with MAOIs and other drugs in animals

In addition to the effects of drugs on DMT tissue levels and metabolism discussed in the previous section, a number of studies have assessed the effects of the interaction of DMT with other drugs on animal behavior and physiological variables. Moore et al. (1975) studied the effects of iproniazid, chlorpromazine and methiothepin on DMT-induced changes in body temperature, pupillary dilatation, blood pressure and EEG in rabbits. In this paper, only three animals were studied and no figures are provided regarding the EEG and pupil diameter data, despite the fact that the authors mention that both variables are modified after DMT and discuss the effects of the various drugs tested on the DMT-induced changes. They conclude that iproniazid had a potentiating action in the effects of DMT, while chlorpromazine and methiothepin antagonized these actions of DMT. Regarding the effects of iproniazid, they conclude that the drug prolonged the mydriatic action of DMT while no data are provided to support this conclusion. Similarly, the authors state that iproniazid prolonged the elevated rectal temperature induced by DMT, but the data do not clearly support this if differences in baseline values are taken into account. Drug effects on blood pressure were not markedly altered by pretreatment with iproniazid. Results from chlorpromazine and methiothepin show that these drugs attenuated DMT-induced hyperthermia and increases in blood pressure. Shah and Hedden (1978) found the MAOI iproniazid prolonged the abnormal behavior induced by DMT, in contrast with the microsomal enzyme inhibitor SKF-525A and the neuroleptic chlorpromazine, which did not alter the effects of DMT administered alone. These authors also found that iproniazid increased drug levels in plasma, brain and liver. They concluded that DMT effects are due to the parent compound and not to a metabolite and that degradation by MAO is the primary metabolic route of DMT in vivo. Finally, Stoff et al. (1982) found the MAOI pargyline to potentiate DMT-induced disruption of conditioned avoidance response in rats.

5.3. DMT interactions with MAOIs and other drugs in humans

The specific question of the interaction of oral DMT with MAO inhibitors has not been evaluated in controlled clinical trials, but valuable information has been obtained by different researchers in single-subject experiments involving the self-administration of drugs. Initial efforts were directed at elucidating whether harmaline could render DMT orally active. Bigwood found that a dose of 100 mg DMT freebase (1.16 mg/kg) taken in combination with

a dose of harmine hydrochloride equivalent to 86 mg freebase (1.0 mg/kg) resulted in distinct psychedelic effects (Bigwood 1978, cited in Ott, 1999). However, given the low concentrations of harmaline relative to those of harmine in *B. caapi* and in *ayahuasca*, Ott (1999) experimented with the oral ingestion of combinations of DMT plus harmine. With this procedure he established the threshold dose of harmine necessary to render DMT orally active at 1.5 mg/kg. At this harmine dose, the threshold for DMT was found at 0.38 mg/kg and doses as high as 2.0 mg/kg were tested. The author found the intensity of effects to be enhanced with increasing doses, while the time course of effects remained the same, resembling that of his self-experiments with *ayahuasca*. In his own words: "45 minutes to an hour incubation period, with effects quickly building to a peak within the next 30 minutes and maintaining a plateau for 45 minutes to an hour, followed by about an hour of diminishing effects; the experience was usually completely over within three hours". Ott expanded these findings to the MAO inhibitor isocarboxazid, which rendered DMT orally active after pretreatment with 30 mg. Other self-experimenters have replicated these results, finding that harmaline alone in doses around 1 mg/kg lacks visionary activity and that both harmine and harmaline at 1.0-1.5 mg/kg doses render various tryptamines such as DMT, 5-MeO-DMT and diethyltryptamine orally active (for a review see Ott, 1999).

The above findings are in clear contrast with an early study in which healthy human volunteers received i.m. doses (two subjects 0.35-0.55 mg/kg and five subjects 0.65-0.83 mg/kg) of DMT following pretreatment with 100 mg of the MAOI iproniazid administered daily for four days (Sai-Halász, 1963). Subjects receiving the DMT low doses following the iproniazid pretreatment period experienced none of the typical visual effects, reporting only a feeling of "strangeness". Those receiving the high doses had a biphasic response. Immediately after drug administration the usual DMT effects were experienced, although less pronounced, and after the first 30 min, they reported a persistent feeling of "strangeness" characterized by indifference and "emotional bleakness" (Sai-Halász, 1963). Thus, while acute MAO inhibition may facilitate DMT absorption and probably reduce its elimination rate by preventing drug metabolism, chronic MAOI administration apparently leads to a reduction in the potency of subjective DMT effects. The mechanism involved remains to be clarified, although Sai-Halász (1963) proposed that enhanced serotonin levels in the CNS may be responsible for this effect.

6. Pharmacology of *B. caapi* β-carbolines in humans

These tricyclic compounds are the most abundant alkaloids in *ayahuasca* potions, and represent the chief contribution of *B. caapi* to the tea. Despite the fact that harmaline has at some stage been considered to be responsible for the psychotropic properties of *ayahuasca* (Naranjo, 1967), the capacity of the β-carbolines to interact with the 5-HT_{2A} receptor and/or their ability to elicit effects in humans analogous to those of the psychedelic tryptamines and phenylethylamines has not been clearly established. Receptor binding and drug discrimination studies have provided inconsistent results, and definitive conclusions cannot be drawn regarding whether certain doses of these drugs, which show varying affinity to the 5-HT_{2A} receptor, elicit in animals interoceptive effects similar to those of the classical psychedelics. In addition, their ability to elicit clear-cut psychedelic effects has been repeatedly contested. The question remains controversial owing to the fact that the pharmacology of β-carbolines has been poorly characterized in humans.

6.1. Subjective effects

The few data available on the subjective effects of ß-carbolines mainly stem from reports of self-experiments and from the clinical studies by Pennes and Hoch (1957), Naranjo (1967), and Slotkin (1970). Information from anecdotal reports makes the classification of the harmala alkaloids as psychedelics doubtful a priori. In their book TIHKAL, Shulgin and Shulgin (1997) cite other researchers' self-experiment reports in which harmine was described as mainly inducing dysphoric physical reactions and some psychological effects which ranged from relaxation (300 mg sublingually) and sedation (140 mg orally) to excitement and restlessness (40 mg orally), belligerency (above 40 mg orally) and "psychotic symptoms" (300-400 mg orally). These reports thus appear to be contradictory, and there seems to be no consistent dose-response pattern that could be derived from these data. In the chapter devoted to harmaline, Shulgin and Shulgin (1997) describe their own self-experiments with the drug. They report experiencing no effects with 100 mg orally, numbness and some modification of auditory perception with 150 mg orally, and visual imagery with eyes closed at 200 mg orally and also at the higher 300-500 mg dose range. At these higher doses nausea and general malaise were very prominent.

Also in self-experiments, Ott found that when 1.5 mg/kg harmine (120 mg), i.e, the threshold dose capable of rendering DMT orally active, was ingested in the absence of DMT, the drug exerted "barely perceptible sedative effects" (Ott, 1999). Based on these observations, the typical visionary effects of *ayahuasca* would appear to be related to the DMT present in the potion rather than to the psychotropic effects of harmine. Self-reports by other authors have described no "notable psychoactive or somatic effect felt" after 0.5 mg/kg harmine taken intranasally and orally (De Smet, 1985, cited in Ott, 1993) or have characterized harmine as "a mild sedative in low doses, causing unpleasant vegetative and neurological symptoms at doses above 300 mg" (Leuner and Schlichting, 1991, cited in Ott, 1993). The same applies to harmaline, which Bigwood found to be inactive after ingesting a 100 mg dose (Bigwood 1978, cited in Ott, 1993).

Pennes and Hoch (1957) administered harmine orally, subcutaneously and intravenously to psychiatric patients, mainly schizophrenics, in doses ranging from 20 to 960 mg. Harmine was described to be hallucinogenic above 150-200 mg intravenously, with 50% of the subjects reporting "visual hallucinations", or rather "hypnagogic imagery or visions", which disappeared with eyes open. Visual hallucinations occurred at medium or high dosage, and shallow euphoria was occasionally observed. The maximum administered i.v. dose was 300 mg. These researchers observed bradycardia and hypotension following i.v. harmine administration. The drug was not found to be hallucinogenic after oral (up to 960 mg) or subcutaneous administration. The authors commented that harmine produced "mental clouding" and drowsiness, in contrast with LSD and mescaline, which they had studied previously.

Naranjo (1967) published a report on the human pharmacology of the harmala alkaloids. While most of the chapter centered basically on harmaline, he also provided some data regarding harmine and THH. According to Naranjo, threshold doses capable of eliciting hallucinogenic activity are 8 mg/kg orally for harmine and 1 mg/kg i.v. or 4 mg/kg orally for harmaline. He further commented that THH appears to be even less active than harmine, with an oral dose of 300 mg *d,l*-THH eliciting subjective effects similar to those of 100 mg of harmaline. Apparently, these studies were conducted in the absence of placebo controls and the author does not provide any information in the paper as to how the intensity of effects was measured in order to establish comparisons between drugs. In the case of the comparison between harmine and THH, data were obtained from only one volunteer. Unfortunately, this

limited report remains to date the primary source of evidence of the psychedelic effects of the harmala alkaloids. In addition to methodological limitations, further doubts on the validity of Naranjo's conclusions arise from the apparent contradiction with results by Pennes and Hoch (1957). Thus, the threshold dose for oral harmine reported by Naranjo (1967), i.e., 8 mg/kg, is below the 960 mg oral dose (aprox. 12 mg/kg in a 70 kg individual) which was found by Pennes and Hoch (1957) to lack hallucinogenic effects. As mentioned above, the main focus of Naranjo's paper was harmaline, the effects of which (orally and i.v. administered) were compared with those of the more prototypical psychedelic mescaline. The study participants were apparently able to distinguish between the effects of harmaline and mescaline. Whereas mescaline induced marked modifications in the environment, this remained unchanged under harmaline. However, following harmaline administration subjects described images superimposed on the surroundings and one participant reported experiencing a true hallucination. Vibration in the visual field and light flashes were also reported. With eyes closed, subjects experienced vivid colorful dream-like images. In contrast with mescaline, auditory perception was not modified, and neither were thought processes, emotions or the rate of time passing. Naranjo (1967) concluded that harmaline appeared to be "more of a pure hallucinogen than other substances" due to its effects targeting primarily visual perception without affecting other spheres of the psyche. He globally described harmine and harmaline as showing a "highly hallucinogenic quality in the visual domain", although harmaline appeared to cause "more withdrawal and lethargy" than harmine.

Slotkin and coworkers (1970) administered i.v. doses of 0.5 mg/kg harmine to five healthy male volunteers. This dose was far below the threshold of hallucinogenic activity reported by Pennes and Hoch (1957) or the amounts administered by Naranjo (1967). Contrary to the observations by the latter, the volunteers in this study did not experience hallucinations or psychedelic effects.

6.2. Pharmacokinetics and metabolism

Slotkin and coworkers (1970) reported a rapid drop in plasma harmine concentrations following the drug's i.v. administration. Similarly to DMT, pharmacokinetic parameter values have never been assessed for these compounds in humans. Regarding metabolism, *O*-demethylation appears to be a major metabolic pathway for *β*-carbolines with a methoxy group in position 7. Harmol glucuronide and harmol sulfate have been described as the main

urinary metabolites of harmine following its i.v. administration to humans and rodents (Slotkin et al., 1970). A very recent study has found cytochrome P450 to catalyze the *O*-demethylation of harmine and harmaline, and has identified CYP2D6 and CYP1A1 as the major isoenzymes involved in the process (Yu et al., 2003). To my knowledge no data are available regarding the metabolism of THH.

6.3. Cardiovascular effects

No systematic controlled study was found in the literature on the cardiovascular effects of the harmala alkaloids. However, Pennes and Hoch (1957) and Slotkin et al (1970) have reported bradycardia and hypotension after acute i.v. administration of harmine.

6.4. Adverse effects

Harmine and harmaline appear to induce a plethora of somatic-dysphoric effects. These have become apparent both in self-experiments and in clinical studies. Thus, Leuner and Schlichting cited "unpleasant vegetative and neurological symptoms" above 300 mg harmine (Leuner and Schlichting, 1991, cited in Ott, 1993). Pennes and Hoch (1957) reported nausea, vomiting, tremor and body numbness, which were very frequent after i.v. administration and in some cases per os with doses above 300-400 mg. Naranjo (1967) reported harmaline appeared to elicit more physical effects than mescaline. Unpleasant effects were mainly paresthesias and numbness, physical discomfort, nausea, intense vomiting and dizziness. Finally, Slotkin et al. (1970) observed "bradycardia, trouble in focussing the eyes, tingling, hypotension, cold extremities and light-headedness".

7. Mechanism of action of β-carbolines

7.1. Receptor level interactions

The receptor binding profile of the β-carbolines has not been evaluated systematically until recent times. Drug displacement studies using [^{3}H]DOB as 5-HT_{2A} ligand showed that the β-carbolines in general bind with modest affinity to this receptor. An exception is harmine which shows nanomolar affinity for this site, a surprisingly similar affinity value to that of DMT (Glennon et al., 2000). These authors studied a series of β-carbolines and found the

following order of decreasing affinity for the 5-HT_{2A} site: harmine > harmaline > *l*-THH > *d*-THH > harmalol (Glennon et al., 2000). Analogous results had been obtained in a previous study using [^{3}H]ketanserin as the labeled radioligand (Grella et al., 1998). In these two studies, affinity for the 5-HT_{2C} site also decreased from the full aromatic harmine, to harmaline and THH, which showed the lowest affinity. Harmine affinity for the 5-HT_{2A} receptor was an order of magnitude greater than for the 5-HT_{2C} site. Furthermore, harmine, harmaline, THH and harmalol showed no relevant affinity for the 5-HT_{1A} receptor, the D_2 dopamine receptor or the benzodiazepine receptor. Only certain compounds with a methoxycarbonil group in position three of the fully aromaticβ-carboline (not present in *B. caapi*) showed any relevant affinity for the benzodiazepine receptor in this study (Glennon et al., 2000), in agreement with previous results by Lippke et al. (1983). Other studies for harmine and harmaline had found low micromolar affinity for the benzodiazepine receptor (Müller et al., 1981; Rommelspacher et al., 1981). A recent study found that β-carbolines show nanomolar affinity for the I_2 imidazoline receptor. Affinity was higher for harmine, intermediate for harmaline and lowest for THH (Husbands et al., 2001). Receptor affinity values for the β-carbolines are shown in Tables 7-10.

Table 7: Harmine radioligand binding data at serotonergic, dopaminergic, benzodiazepine, muscarinic cholinergic, opioid, imidazoline and adrenergic receptors.

	K_i (nM)									
	5-HT_{2A}	**5-HT_{2C}**	**5-HT_{1A}**	**D_2**	**BZD**	**Musc.**	**Opioid**	**I_2**	**I_1**	**α_2**
Husbands et al., 2001[a]								10	-	>10,000
Glennon et al., 2000[b]	397	5,340	>10,000	>10,000	>10,000	-	-	-	-	-
Grella et al., 1998[c]	230	5,340	-	-	-	-	-	-	-	-
	IC_{50} (nM)									
Husbands et al., 2001[a]	-	-	-	-	-	-	-	-	629	-
Müller et al., 1981[d]	-	-	-	69,000	134,000	5,000	7,000	-	-	-

D_2=Dopamine-2, BZD=benzodiazepine, Musc.=muscarinic cholinergic, I_1=Imidazoline-1, I_2=Imidazoline-2, α_2=α_2-adrenergic. (-) = not determined.

[a] Radioligands: [^{3}H]clonidine + rauwolscine (Imidazoline I_1), [^{3}H]2BFI (Imidazoline I_2), [^{3}H]RX821002 (α_2-adrenoceptor).

[b] Radioligands: [^{3}H]DOB (5-HT_{2A}), [^{3}H]8-OH DPAT (5-HT_{1A}), [^{3}H]Mesulergine (5-HT_{2C}), [^{3}H]N-methylspiperone (D_2), [^{3}H]RO15,1788 (BZD).

[c] Radioligands: [^{3}H]Ketanserin (5-HT_{2A}), [^{3}H]Mesulergine (5-HT_{2C}).

[d] Radioligands: [^{3}H]Spiperone (D_2),[^{3}H]Flunitrazepam (BZD), [^{3}H]Quinuclidinylbenzylate (QNB, Muscarine Cholinergic), [^{3}H]Naloxone (Opioid).

Table 8: Harmaline radioligand binding data at serotonergic, dopaminergic, benzodiazepine, muscarinic cholinergic, opioid, imidazoline and adrenergic receptors.

	K_i (nM)									
	5-HT$_{2A}$	**5-HT$_{2C}$**	**5-HT$_{1A}$**	**D$_2$**	**BZD**	**Musc.**	**Opioid**	**I$_2$**	**I$_1$**	**α_2**
Husbands et al., 2001[a]	-	-	-	-	-	-	-	22	-	>10,000
Glennon et al., 2000[b]	5,010	9,430	>10,000	>10,000	>10,000	-	-	-	-	-
Grella et al., 1998[c]	7,790	9,430	-	-	-	-	-	-	-	-
Helsley et al., 1998b[d]	42,500	-	-	-	-	-	-	-	-	-
	IC_{50} (nM)									
Husbands et al., 2001[a]	-	-	-	-	-	-	-	-	13,800	-
Müller et al., 1981[e]	-	-	-	207,000	390,000	52,000	13,000	-	-	-
Rommelspacher et al., 1981[f]	-	-	-	-	390,000	-	-	-	-	-

D_2=Dopamine-2, BZD=benzodiazepine, Musc.=muscarinic cholinergic, I_1=Imidazoline-1, I_2=Imidazoline-2, α_2=α_2-adrenergic. (-) = not determined.

[a] Radioligands: [^{3}H]clonidine + rauwolscine (Imidazoline I_1), [^{3}H]2BFI (Imidazoline I_2), [^{3}H]RX821002 (α_2-adrenoceptor).

[b] Radioligands: [^{3}H]DOB (5-HT$_{2A}$), [^{3}H]8-OH DPAT (5-HT$_{1A}$), [^{3}H]Mesulergine (5-HT$_{2C}$), [^{3}H]N-methylspiperone (D_2), [^{3}H]RO15,1788 (BZD).

[c] Radioligands: [^{3}H]Ketanserin (5-HT$_{2A}$), [^{3}H]Mesulergine (5-HT$_{2C}$).

[d] Radioligand: [^{3}H]Ketanserin (5-HT$_{2A}$).

[e] Radioligands: [^{3}H]Spiperone (D_2),[^{3}H]Flunitrazepam (BZD), [^{3}H]Quinuclidinylbenzylate (QNB, Muscarine Cholinergic), [^{3}H]Naloxone (Opioid).

[f] Radioligand: [^{3}H]Flunitrazepam (BZD)

Table 9: THH radioligand binding data at serotonergic, dopaminergic, benzodiazepine, muscarinic cholinergic, opioid, imidazoline and adrenergic receptors.

	K_i (nM)									
	5-HT$_{2A}$	**5-HT$_{2C}$**	**5-HT$_{1A}$**	**D$_2$**	**BZD**	**Musc.**	**Opioid**	**I$_2$**	**I$_1$**	**α_2**
Husbands et al., 2001[a]	-	-	-	-	-	-	-	172	-	-
Glennon et al., 2000[b]	>10,000	>10,000	>10,000	-	-	-	-	-	-	-
Grella et al., 1998[c]	>10,000	>10,000	-	-	-	-	-	-	-	-
	IC_{50} (nM)									
Husbands et al., 2001[a]	-	-	-	-	-	-	-	-	2650	-

D_2=Dopamine-2, BZD=benzodiazepine, Musc.=muscarinic cholinergic, I_1=Imidazoline-1, I_2=Imidazoline-2, α_2=α_2-adrenergic. (-) = not determined.

[a] THH enantiomer tested not specified, presumably racemic mixture. Radioligands: [^{3}H]clonidine + rauwolscine (Imidazoline I_1), [^{3}H]2BFI (Imidazoline I_2), [^{3}H]RX821002 (α_2-adrenoceptor).

[b] R(+) enantiomer of THH tested. Radioligands: [^{3}H]DOB (5-HT$_{2A}$), [^{3}H]8-OH DPAT (5-HT$_{1A}$), [^{3}H]Mesulergine (5-HT$_{2C}$), [^{3}H]N-methylspiperone (D_2), [^{3}H]RO15,1788 (BZD).

[c] R(+) enantiomer of THH tested. Radioligands: [^{3}H]Ketanserin (5-HT$_{2A}$), [^{3}H]Mesulergine (5-HT$_{2C}$).

Table 10: Harmalol radioligand binding data at serotonergic, dopaminergic, benzodiazepine, muscarinic cholinergic, opioid, imidazoline and adrenergic receptors.

	K_i (nM)									
	5-HT_{2A}	**5-HT_{2C}**	**5-HT_{1A}**	**D_2**	**BZD**	**Musc.**	**Opioid**	**I_2**	**I_1**	**α_2**
Husbands et al., 2001[a]	-	-	-	-	-	-	-	132	-	-
Glennon et al., 2000[b]	>10,000	>10,000	>10,000	-	-	-	-	-	-	-
	IC_{50} (nM)									
Husbands et al., 2001[a]	-	-	-	-	-	-	-	-	1591	-

D_2=Dopamine-2, BZD=benzodiazepine, Musc.=muscarinic cholinergic, I_1=Imidazoline-1, I_2=Imidazoline-2, α_2=α_2-adrenergic. (-) = not determined.
[a] Radioligands: [^{3}H]clonidine + rauwolscine (Imidazoline I_1), [^{3}H]2BFI (Imidazoline I_2), [^{3}H]RX821002 (α_2-adrenoceptor).
[b] Radioligands: [^{3}H]DOB (5-HT_{2A}), [^{3}H]8-OH DPAT (5-HT_{1A}), [^{3}H]Mesulergine (5-HT_{2C}), [^{3}H]N-methylspiperone (D_2), [^{3}H]RO15,1788 (BZD).

The visionary effects reported for the β-carbolines by Naranjo (1967) would well fit an interaction with the 5-HT_{2A} receptor. It is interesting, however, that Naranjo found harmaline to be more potent than harmine in humans, but it is the latter that shows the highest affinity for the 5-HT_{2A} sites in receptor binding studies. Results from drug discrimination studies and phosphoinositide hydrolysis regarding the β-carbolines are also contradictory. While DOM stimulus has been found to generalize to harmaline, it does not appear to generalize to harmine (Glennon et al., 1983b), and results for harmaline are not very consistent either. Harmaline has recently been found not to substitute for LSD in the drug-discrimination paradigm (Helsley et al., 1998a) in line with results by Nielsen and coworkers (1982) who only found a maximum of 54% appropriate responding for harmaline. In addition to these inconsistent findings, none of the β-carbolines has been found to stimulate phosphoinositide hydrolisis (Glennon et al., 2000), in clear opposition with the phenylethylamines and indolalkylamines, which behave as partial agonists in this model (see section 4.1.). These results, considered together with the equal affinity shown by harmine to agonist- and antagonist-labeled 5-HT_{2A} receptors (Glennon et al., 2000; Grella et al., 1998), question the assumption that these compounds act as agonists at this receptor.

In summary, based on the limited data available today, the question whether the β-carbolines in general activate the 5-HT_{2A} receptor remains unanswered. In addition, given the

contradictory nature of the reports on the subjective effects of the β-carbolines, the pharmacology of these compounds in humans would need to be reexamined before any final conclusions can be drawn on their potential as psychedelics.

7.2. The β-carbolines as MAO inhibitors

The one pharmacological action some β-carbolines, especially harmine and harmaline, seem to display beyond doubt is their ability to inhibit the enzyme monoamine oxidase at concentrations in the micromolar and nanomolar range. As indicated in section 4.2., MAO is a mitochondrial enzyme involved in the inactivation of biogenic amines. The enzyme actually occurs as two isoforms, A and B, found throughout the body, which catalyze the oxidative deamination of different endogenous (neurotransmitters) and exogenous substrates. Both MAO isoforms are found in high levels in the human brain but also in peripheral organs such as the liver (Saura et al., 1996). The proportion of the different isoforms in a given organ shows marked interspecific variations. Thus, while human and rat liver show high MAO-A activity (in addition to MAO-B activity), non-human primate liver is devoid of MAO-A activity (Inoue et al., 1999). Studies reporting on the potency of MAO inhibitors in general and of the β-carbolines in particular may provide different IC_{50} values depending on the MAO source tissue (richer in the A or B form) and the substrate used (which can be unspecific or show selective affinity for one of the two isoforms). Two commonly used substrates, tyramine and tryptamine have been found to be substrates of both isoenzymes A and B, while β-phenylethylamine is predominantly a substrate of MAO-B. Regarding the oxidative deamination of psychedelic tryptamines and more specifically of DMT, the existing evidence indicates that the drug is a substrate of both isoforms at low concentrations, with probably a greater affinity for MAO-B at higher concentrations (Suzuki et al., 1981).

Initial studies found that certain tetrahydro-β-carbolines could inhibit the oxidative deamination of serotonin by MAO (Freter et al., 1958). Subsequently, Undenfriend and coworkers (1958) demonstrated that harmine, harmaline and THH behaved in vitro as MAO inhibitors. In addition, harmaline was also tested and shown to be active in vivo. Furthermore, these authors also demonstrated that harmaline inhibited MAO through a competitive and reversible mechanism. These findings were replicated in subsequent studies conducted by other researchers.

Yashuhara et al. (1972) found harmine exhibited different efficiency in MAO inhibition depending on the substrate used. Thus, harmine was more effective at inhibiting serotonin oxidation than tyramine oxidation. Furthermore, in a subsequent study this author found that harmine was much more effective at inhibiting either serotonin or tyramine oxidation by brain MAO than by beef liver MAO, pointing out that different isoenzymes predominate in each organ (Yashuhara, 1974). Similarly, Fuller et al. (1972) demonstrated harmaline was far more effective at inhibiting the MAO isoform capable of degrading serotonin than the isoform degrading phenylethylamine. Thus, *β*-carbolines appear to be more effective inhibitors of MAO-A, of which serotonin is a substrate, than MAO-B.

Using tyramine as substrate, McIsaac and Estevez (1966) studied structure-activity relationshipss in a series of *β*-carbolines and found the degree of saturation of the pyridine ring to influence the potency of these compounds as MAO inhibitors. Tetrahydro-derivatives were found to be the least active, dihydro-derivatives showed intermediate potency and the fully aromatic compounds were the most active. Thus, harmine was two orders of magnitude more potent than harmaline. Harmol and harmalol were equipotent with harmine. In this study THH was not tested.

Buckholtz and Boggan (1977a) conducted a study including harmine, harmaline, THH and their *O*-demethylated analogues harmol, harmalol, and tetrahydroharmol. Structure-activity relationships were studied using tryptamine as substrate and MAO obtained from mouse brain as the MAO source. Results replicated the findings by McIsaac and Estevez in liver (1966) indicating that the aromatic and dihydro-derivatives are more potent than the tetrahydro-derivatives. In this study the hydroxylated derivatives were several orders of magnitude weaker than their methoxylated counterparts. Another interesting finding was the higher potency showed by harmaline at inhibiting oxidation of serotonin than oxidation of *β*-phenylethylamine both in vitro and in vitro, again suggesting a greater selectivity for MAO-A than for MAO-B.

In a recent in vivo study, intraperitoneal administration of harmine to rats dose-dependently increased brain levels of dopamine and reduced the levels of the deaminated monoamine metabolites of dopamine 3,4-dihydroxyphenylacetic acid (DOPAC), norepinephrine homovanillic acid (HVA) and serotonin 5-hydroxyindoleacetic acid (5-HIAA) in a similar fashion to moclobemide, confirming the MAOI effects of systemically administered harmine

(Iurlo et al., 2001). Table 11 shows IC_{50} and K_i estimates for MAO inhibition by various β-carbolines.

Table 11: IC_{50} and K_i values for MAO inhibition by β-carbolines

Harmine	**Tissue**	**Substrate**	**IC_{50}**	**Study**
	Rat liver homogenate	Serotonin	$1.0x10^{-6}$	Undenfriend et al., 1958
	Calf liver mitochondrial fraction	Tyramine	$1.5x10^{-8}$	McIsaac & Estevez, 1966
	Beef brain mitochondrial fraction	Serotonin	$3.0x10^{-7}$	Yasuhara, 1974
	Beef brain mitochondrial fraction	Tyramine	$3.0x10^{-3}$	Yasuhara, 1974
	Mouse whole brain homogenate	Tryptamine	$8.0x10^{-8}$	Buckholtz & Boggan, 1977a
	Rat liver cytosol	Tryptamine	$1.3x10^{-8}$	McKenna et al., 1984
	Tissue	**Substrate**	**K_i**	**Study**
	Pure human liver MAO-A	Kynuramine	$5.0x10^{-9}$	Kim et al., 1997
Harmaline	**Tissue**	**Substrate**	**IC_{50}**	**Study**
	Rat liver homogenate	Serotonin	$1.0x10^{-6}$	Undenfriend et al., 1958
	Calf liver mitochondrial fraction	Tyramine	$1.0x10^{-6}$	McIsaac & Estevez, 1966
	Mouse whole brain homogenate	Tryptamine	$6.0x10^{-8}$	Buckholtz & Boggan, 1977a
	Rat liver cytosol	Tryptamine	$1.6x10^{-8}$	McKenna et al., 1984
	Tissue	**Substrate**	**K_i**	**Study**
	Pure human liver MAO-A	Kynuramine	$48.0x10^{-9}$	Kim et al., 1997
THH	**Tissue**	**Substrate**	**IC_{50}**	**Study**
	Rat liver homogenate	Serotonin	$1.0x10^{-5}$	Undenfriend et al., 1958
	Mouse whole brain homogenate	Tryptamine	$1.4x10^{-5}$	Buckholtz & Boggan, 1977a
	Rat liver cytosol	Tryptamine	$1.8x10^{-6}$	McKenna et al., 1984
Harmol	**Tissue**	**Substrate**	**IC_{50}**	**Study**
	Calf liver mitochondrial fraction	Tyramine	$2.8x10^{-8}$	McIsaac & Estevez, 1966
	Mouse whole brain homogenate	Tryptamine	$5.8x10^{-6}$	Buckholtz & Boggan, 1977a
	Rat liver cytosol	Tryptamine	$5.0x10^{-7}$	McKenna et al., 1984
Harmalol	**Tissue**	**Substrate**	**IC_{50}**	**Study**
	Calf liver mitochondrial fraction	Tyramine	$2.5x10^{-8}$	McIsaac & Estevez, 1966
	Mouse whole brain homogenate	Tryptamine	$1.0x10^{-5}$	Buckholtz & Boggan, 1977a
THH-OH	**Tissue**	**Substrate**	**IC_{50}**	**Study**
	Mouse whole brain homogenate	Tryptamine	$1.0x10^{-5}$	Buckholtz & Boggan, 1977a

7.3. The β-carbolines as monoamine reuptake inhibitors

Buckholtz and Boggan (1977b) studied the effects of β-carbolines on monoamine reuptake into mouse brain synaptosomes. These researchers found that these compounds inhibited the reuptake of serotonin at micromolar concentrations. Contrary to MAOI activity, tetrahydro-derivatives were more potent than their dihydro- or aromatic counterparts (see Table 12).

Table 12: IC_{50} for monoamine reuptake inhibition by β-carbolines.

	IC_{50} (μM)			
Compound	**^{3}H-Serotonin (3.0 nM)**	**^{3}H-Serotonin (0.1 μM)**	**^{3}H-NE (0.1 μM)**	**^{3}H-DA (0.1 μM)**
Harmine	11	41	22	16
Harmaline	15	-	-	-
THH	3.4	-	-	-
Harmol	17	-	-	-
Harmalol	13	-	-	-
THH-OH	21	-	-	-

Taken from Buckholtz and Boggan (1977b). (-) = not determined.

7.4. Other pharmacological effects

As shown above, the β-carbolines demonstrate a marked variation in their receptor interaction characteristics and pharmacological activity depending on their degree of saturation of the pyridine ring and on their substituents. Besides their MAO inhibitory activity, harmine and harmaline are notorious for their tremorigenic effects (Fuentes and Longo, 1971; Kawanishi et al., 1994). β-carboline-induced tremor has been related to drug interactions with serotonergic and noradrenergic neurotransmission but more prominently with inverse agonist activity at the benzodiazepine receptor. However, as discussed above, contrary to other β-carbolines with alkyloxycarbonil substituents, harmine and harmaline display little affinity for the benzodiazepine receptor and their behavioral and neurochemical effects in animals are not counteracted by flumazenil (Auta et al., 1997; Iurlo et al., 2001). In the specific case of harmaline, tremor has been related to activation of neurons in the inferior olivary nucleus. At high doses, this effect has been found to exert excitotoxicity on Purkinje cells in the cerebellum (O'Hearn and Molliver, 1993). Very recent research has demonstrated the

involvement of glutamate NMDA receptors in the tremor-inducing effects of this drug. The noncompetitive NMDA channel blocker dizocilpine was able to suppress the tremorigenic activity of harmaline (Du and Harvey, 1997). These authors postulated that harmaline may produce tremor by acting as an inverse agonist at the MK-801 binding site in the NMDA channel (Du et al., 1997).

8. The β-carboline-DMT interaction hypothesis in *ayahuasca*

Agurell and coworkers (1968) examined the alkaloid content of *Diplopterys cabrerana* (reported as *Banisteriopsis rusbyana*), a common plant admixture to *ayahuasca*, by means of gas chromatography coupled to mass spectrometry and confirmed previous findings by Poisson (1965) that the plant contained substantial amounts of DMT. At that time, it had already been reported that DMT was inactive orally (Szára, 1957; Turner and Merlis, 1959) and the authors postulated that "The combination in yajé of monoamine oxidase inhibiting harman alkaloids with N,N-dimethyltryptamine might result in specific pharmacological effects" (Agurell et al., 1968). In the same issue of the American Journal of Pharmacy, Der Marderosian and coworkers (1968) replicated the finding and noted that "both the harman alkaloids and DMT are monoamine oxidase inhibitors", and speculated that "perhaps the strong concentration of the active principles or the presence of other unidentified substances facilitate absorption". Since these early works, the interaction hypothesis involving MAO inhibition has been widely accepted and the MAO inhibitory effects of the β-carbolines, *ayahuasca* brews and of an *ayahuasca* analogue obtained by combining pure compounds have been demonstrated in vitro (McKenna et al., 1984). However, MAO inhibition after *ayahuasca* in vivo has not been evaluated to date in humans either by assessing monoamine metabolite levels in plasma or urine or by determining platelet MAO activity.

9. Pharmacology of *ayahuasca* in humans

In 1993, McKenna, Grob, Callaway and other researchers conducted the field phase of a study evaluating the effects of *ayahuasca* in humans who regularly ingest the tea (McKenna et al., 1998). To my knowledge, this is the first attempt to systematically characterize the pharmacology of *ayahuasca* in humans. Acute effects after drug administration were assessed and also several parameters (neurochemical and neuropsychological) were evaluated in long term ritual users. The acute-effect study generated data on the pharmacokinetics of *ayahuasca*

alkaloids and provided information on the subjective, cardiovascular and neuroendocrine effect of the tea following the administration of a single dose. This was an open-label, non-placebo-controlled study in which drug-induced pharmacodynamic changes were referred to baseline values. The *ayahuasca* dose administered by Callaway and coworkers (1999) contained the following average (range) amounts of alkaloids in mg: 35.5 (28.8-43.2) for DMT, 252.3 (204.0-306.0) for harmine, 29.7 (24.0-36.0) for harmaline, and 158.8 (128.4-196.6) for THH. The findings of this study are described in the following sections.

9.1. Subjective effects

In all 15 participants, the administered *ayahuasca* dose was described as eliciting an experience in which "peak plasma levels of DMT were associated with intricate and colored eyes-closed visual imagery, complex thought processes and a general state of heightened awareness". The authors also comment that "overall perceptual, cognitive and affective processes were significantly modified while maintaining the presence of a clear sensorium" (Callaway et al., 1999). A quantitative measure of the intensity of subjective effects was also obtained by means of the Hallucinogen Rating Scale. In general terms, scores were found to be low when compared with prior data obtained after i.v. DMT administration. Thus, the administered 0.48 mg DMT/kg dose yielded scores on the Intensity, Affect, Cognition and Volition comparable to those obtained after 0.1–0.2 mg i.v. DMT/kg. Scores on the Perception scale corresponded to an i.v. dose of 0.1 mg DMT/kg and scores on the Somaesthesia scale were even lower than those of an i.v. dose of 0.05 mg DMT/kg (Grob et al., 1996).

9.2. Pharmacokinetics

Following the oral administration of *ayahuasca*, DMT plasma levels were detected in all volunteers and were high enough to calculate pharmacokinetic parameters in 12. Harmaline levels were very low and allowed the calculation of parameters for only 5 volunteers. In the case of harmine and THH, these were calculated for 14 volunteers. The calculated C_{max}, t_{max}, elimination halflife ($t_{1/2}$), clearance and apparent volume of distribution are shown below.

Table 13: Pharmacokinetic parameters of *ayahuasca* alkaloids expressed as mean (SD)

Alkaloid	C_{max} (ng/ml)	T_{max} (min)	$t_{1/2}$ (min)	Cl/F (ml/min . kg)	V_{ss}/F (l/kg)
DMT	15.8 (4.4)	107.5 (32.5)	259.4 (207.4)	221.8 (129.9)	54.8 (14.8)
Harmine	114.8 (61.7)	102.0 (58.3)	115.6 (60.1)	271.7 (180.3)	49.6 (40.4)
Harmaline	6.3 (3.1)	145.0 (66.9)	-	-	-
THH	91.0 (22.0)	174.0 (39.6)	531.9 (290.8)	63.3 (21.9)	43.5 (8.0)

Taken from Callaway et al. (1999). (-) = not determined.

9.3. Cardiovascular effects

Ayahuasca was found to increase systolic blood pressure, diastolic blood pressure and heart rate over pre-drug baseline values. These pressor and chronotropic effects were not particularly intense, with mean increases of 11 mm Hg for systolic blood pressure, 9.3 for diastolic blood pressure and a maximum mean increase of 7.4 bpm in heart rate. Systolic and diastolic blood pressure increases peaked at 40 min postadministration and returned to baseline values at 3 h postadministration. The peak increase in heart rate was observed at 20 min. Return to baseline values was observed at 4 h after dosing.

9.4. Autonomic effects

Ayahuasca administration had mydriatic effects, increasing pupil diameter 1 mm in relation to preadministration values. This increase was maximum at 3 h postadministration and returned to baseline values at 6 h. Respiratory frequency was also found to increase with *ayahuasca*. This variable fluctuated showing increases and decreases, with a maximum mean increase of 3.1 breaths per min at 90 min postadministration. Body temperature also increased reaching a maximum mean increase of 0.3 ºC at 4 h after dosing.

9.5. Neuroendocrine effects

Following *ayahuasca* administration, plasma levels of cortisol, prolactin and growth hormone increased from baseline values. Peak increases were found at 60 min for cortisol, at 120 min for prolactin and at 90 min for growth hormone. Levels returned to baseline or below baseline (cortisol) at 6 h postadministration.

9.6. Adverse effects

Callaway and coworkers (1999) comment that nausea, vomiting and diarrhea are not uncommon following *ayahuasca* consumption. In fact one of the volunteers enrolled in this study vomited 45 min after receiving an oral dose of the tea. In the course of the clinical trial, nystagmus and tremor were also observed. Other adverse events associated with acute *ayahuasca* intake reported in the scientific literature include intense fear in the course of a self-experience with the tea described by one researcher (Rivier and Lindgren, 1972). Finally Callaway and Grob (1998) have warned against possible interactions between *ayahuasca* alkaloids and serotonin reuptake inhibitors. They report a case study in which the concomitant use of both drugs led to a syndrome characterized by loss of consciousness, motor tremors and severe nausea and vomiting.

9.7. Long term effects

Callaway and coworkers (1994) examined the effects of long-term ingestion of *ayahuasca* on serotonergic neurotransmission by means of a peripheral marker. They studied the binding of [^{3}H]citalopram to the platelet serotonin transporter. The authors found an increase in the number of platelet binding sites relative to *ayahuasca*-naive individuals, and no change in the dissociation constant. No definite explanation was given for this finding, but in a later study utilizing Single Photon Emission Computerized Tomography (SPECT), one of the researchers of the study found his own levels of cerebral serotonin transporter to be increased in the prefrontal cortex after six weeks of daily dosing with THH. These findings suggest that serotonergic neurotransmission undergoes a modulation which lasts beyond the acute effects of *ayahuasca*. Furthermore, these changes appear to be related with THH and seem to be reversible, since the cerebral levels of the serotonin transporter returned to baseline levels after THH was discontinued (McKenna et al., 1998). Whether this modulation also takes place in the brains of regular *ayahuasca* users, and the therapeutic or pathological implications of these changes remain unknown.