Chapter 1
Ayahuasca as a Versatile Therapeutic Agent: From Molecules to Metacognition and Back

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N,N-Dimethyltryptamine, β-carboline Alkaloids, and the Biochemical Effects of Ayahuasca

One of the most common versions of ayahuasca tea available globally comes from a mix of *Banisteriopsis caapi* (Malpighiaceae) and *Psychotria viridis* (Rubiaceae) (McKenna, Towers & Abbott, 1984). Based on published reports (Dos Santos et al., 2011, 2012; Riba et al., 2001, 2003; Sanches et al., 2016), this combination appears to be reasonably safe, in terms of its physiological impact, when administered to healthy individuals.

B. caapi contains β-carboline alkaloids; mainly harmine, tetrahydroharmine (THH), and to a lesser extent, harmaline (McKenna et al. 1984; Rivier & Lindgren, 1972). *P. viridis* contains N,N-Dimethyltryptamine (DMT), which is orally inactive

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due to its transformation by monoamine oxidase (MAO) activity in the gastrointestinal tract. Since β-carboline alkaloids are MAO inhibitors (Ott, 1999; Wang et al., 2010), they prevent DMT degradation, thereby allowing DMT to enter the general circulatory and central nervous systems (Bouso & Riba, 2014; McKenna, et al. 1984), where they can produce psychoactive effects (Szára, 1956).

The indole psychedelic DMT has long been considered to play a major role in the pharmacology of ayahuasca. DMT shows serotoninergic agonist activity at the 5-HT2A and 5-HT1A receptors sites (González-Maeso & Sealfon, 2009) and induces brief but intense modifications of the ordinary state of awareness (Strassman, Qualls, Uhlenhuth & Kellner, 1994; Riba et al., 2002). DMT also interacts with the intracellular sigma-1 receptor (S1R) (Fontanilla et al., 2009), which modulates the activity of other proteins and promotes neural plasticity (Chu & Ruoho, 2016; Tsai et al., 2009).

In mice, DMT blocks sodium channels and induces hypermobility (Fontanilla et al., 2009). DMT is also an agonist at the trace amine associated receptor (TAAR) (Bunzow et al., 2001), which has been reported to have a potential role in schizophrenia, fibromyalgia, affective disorders, addiction, drug abuse, and Parkinson's disease (Berry, Gainetdinov, Hoener & Shahid, 2017). TAAR was initially discovered through a search for novel 5HT receptors (Borowsky et al., 2001). DMT is also a substrate of the vesicle monoamine and serotonin transporters (Cozzi et al., 2009). A recent study (Szabo et al., 2016) found that DMT-mediated S1R mitigates hypoxic stress of in vitro-cultured human cortical neurons, monocyte-derived macrophages, and dendritic cells, and increases their survival. Hence, downregulation of S1R abrogates DMT-mediated effects on cellular survival and hypoxia-inducible factor 1-alpha (HIF-1a) expression in hypoxic in vitro cultures of human primary cells.

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Another proposed mechanism for DMT-mediated S1R modulation is that S1R activation would, in turn, modulate Ca2+ signaling, thereby altering the function of intracellular kinases involved in cellular survival. These results suggest a novel and important role for DMT in human cellular physiology, indicating the potential value of DMT-mediated S1R modulation in future therapies targeted at hypoxia/ischemia-related pathologies.

The main constituent of the *B. caapi* vine and the principal ingredient—together with DMT—of ayahuasca preparation is the β-carboline alkaloid harmine. It is still unclear if orally ingested harmine in ayahuasca or related β-carboline alkaloids (THH and harmaline), produces psychoactive or hallucinogenic effects (Dos Santos & Hallak, 2016; Dos Santos, Bouso & Hallak, 2017). In fact, studies in humans have shown inconclusive results, describing sedative-like effects or even a lack of psychoactive effects instead of hallucinogenic (see Dos Santos, Bouso & Hallak 2017). Interestingly, a study conducted in healthy volunteers showed that the β-carbolines (including harmine) are associated with specific electroencephalographic (EEG) alterations, suggesting central/psychoactive effects (Schenberg et al., 2015).

In rodents, harmine improves memory and learning-related deficits in an object recognition task (short-term memory), the MM test (spatial memory), and a delayed match-to-sample asymmetrical 3-choice water maze task. This has been supported by improvements in several biochemical parameters in the rodent hippocampus and in hippocampal cell cultures. Besides, harmine could also induce neuroprotective effects by inhibiting DYRK1A, a protein implicated in neuronal development and apparently involved in abnormal brain development and memory and learning deficits in Alzheimer's and Parkinson's disease and in Down syndrome (Frost et al., 2011; Göckler et al., 2009). According to a recent in vitro study (Li et al., 2017), both harmaline and harmine could potentially be used to treat Alzheimer's disease, Parkinson's disease, depression, and other central nervous system diseases. However, harmine appears to be a multidrug resistance-associated protein isoform2 (MRP2) substrate (it would upregulate its expression) and would be easier metabolized than harmaline, eventually leading to low oral bioavailability (Li et al., 2017). Other preclinical studies show that β-carbolines have affinity for 5-HT2A/2 C receptors (Glennon et al., 2000).

It is not clear if the antidepressant and antiaddictive properties of ayahuasca are related to the pharmacological properties of harmine or DMT, or to a combination of these (Dos Santos, Osório, Crippa, & Hallak, 2016a; Dos Santos et al., 2016b). Future research should assess the role of other molecular mechanisms, such as S1R agonism, in the perceptual, affective, and cognitive effects of DMT and ayahuasca. Given that certain antidepressants (e.g., fluvoxamine) stimulate the S1R, it is plausible that the antidepressant effects recently reported for ayahuasca (Osório et al., 2015; Palhano-Fontes et al., 2017; Sanches et al., 2016) are mediated, at least in part, by S1R agonism.

Neurobiological Effects of Ayahuasca

Some areas implicated in cognitive control, emotion, and memory, such as the insula, the amygdala, and the hippocampus, have been reported to increase blood flow under the effects of ayahuasca (Riba et al., 2006). Other studies have identified the mediotemporal lobe (MTL), which includes the hippocampus, amygdala, and parahippocampal regions, as a target of ayahuasca-induced experience (de Araujo et al., 2012; Riba, Anderer, Jané, Saletu, & Barbanoj, 2004; Riba et al., 2006). The posterior cingulated cortex (PCC) is a key node of the default mode network (DMN) (Raichle et al., 2001). Hyperactivity in this region has been associated with psychopathology (e.g., rumination in depression) (Dutta et al., 2014). DMN is a set of functionally and structurally connected brain regions that are typically deactivated during the performance of externally oriented attention-demanding tasks. This area also exhibits high cerebral blood flow and oxygen consumption during the resting state (Lin et al., 2017).

During the acute phase of ayahuasca, studies have shown that most of the DMN exhibits decreased activity and the PCC shows reduced connectivity (Palhano-Fontes et al., 2015). The spatial brain distribution of ayahuasca-induced changes in the brain has been assessed with low-resolution electromagnetic tomography (LORETA) and EEG recordings. Riba, et al. (2004) reported a decrease of power density in the alpha-2, delta, and beta-1 frequency bands predominantly over the temporo-parieto-occipital junction, whereas theta power was reduced in the temporomedial cortex and in frontomedial regions after ayahuasca intake. These areas comprise the unimodal association cortex, multimodal association cortex, and limbic regions involved in the integration of multimodal sensory information, emotion, and memory processes (Riba et al., 2004).

Ayahuasca has also showed an excitatory effect on cortical regions involved in the processing of visual sensory information (alpha-occipital), memory-affect (MTL), and cognition-affect (theta-frontolateral and frontomedial cortex) (Valle et al., 2016). Randomized clinical trials with experienced psychedelic users suggest a prominent role for the 5-HT2A receptor in the neurophysiological and visionary effects of this substance. Ayahuasca induced significant psychedelic effects and power decreases in the delta-alpha frequency range; decreases in alpha-band oscillations were in posterior brain regions and correlated with the intensity of the visual modifications. The placebo (ketanserin) used in that study blocked these decreases and reduced this correlation.

Another study of our group (Alonso, Romero, Mananas, & Riba, 2015) assessed ayahuasca-induced changes in the dynamic interaction of brain oscillations and the directionality of drug-induced modifications using transfer entropy (TE). That study consisted of 10 healthy volunteers with previous experience in psychedelic drug use. The authors found a reduced density in the medial posterior (precuneus and cuneus) areas and in the ACC.

Similar findings have been observed using magnetoencephalography (MEG) after psilocybin administration, which modified the interaction dynamics between the higher order frontal regions and the more sensory-selective posterior areas (Muthukumaraswamy et al., 2013). 5-HT2A agonism is considered a key mechanism in modifying ayahuasca-induced brain dynamics (McKenna & Riba, 2015). Modifications in the information transfer imply that the predictability of activity in posterior areas (based on information available at anterior sites) decreases while, conversely, the predictability of activity in anterior areas increases (when information is taken into account at posterior sites). Furthermore, in the study by Alonso et al. (2015), these neurophysiological changes, which were related to a reduced top-down control and increased bottom-up information transfer in the brain, were correlated with DMT plasma concentrations and the perceived intensity of psychedelic effects.

The effects of ayahuasca on long-term ayahuasca users have also been examined. The magnetic resonance imaging (MRI) study of Bouso et al. (2015) found an association with opposite changes in brain structure in the anterior and posterior cingulate cortices. Findings included: (a) a decrease in cortical thickness in the PCC and neighboring areas, and (b) an increase in cortical thickness in the medial frontal lobes, specifically in the ACC.

Studies with radiotracer data—mainly Single Photon Emission Computed Tomography (SPECT)— have also been carried out. In a randomized double-blind clinical trial (Riba et al., 2006) increased blood perfusion in the anterior insula (bilaterally) was reported, with greater intensity in the right hemisphere, and in the anterior cingulate/frontomedial cortex (another region of the DMN) of the right hemisphere. Additional increases were observed in the left amygdala/parahippocampal gyrus. Another study (Sanches et al., 2016) found increased blood perfusion in the left nucleus accumbens, the right insula and the left subgenual area; all areas implicated in the regulation of mood and emotions. There are no reports examining the effects of ayahuasca with Positron Emission Tomography (PET) up to date.

The visual network is an area rich in 5-HT2A receptors (Savli et al., 2012). After ayahuasca intake, users are aware that the visions which disappear when opening their eyes and when attention is directed to external cues, are drug-induced (Riba et al., 2001). The visionary phenomena experienced by participants with eyes closed may be attributable to the suppression of inhibitory alpha in the visual network (Valle et al., 2016). Despite their vividness, these images clearly differ from "true hallucinations" (Riba et al., 2001), a state of awareness characterized by dream-like visions more than a pathological distortion of perception. A previous neuroimaging study found increased activity in the visual cortex under ayahuasca (de Araujo et al., 2012). According to Sampedro et al. (2017), visual areas show increased coupling with the PCC but reduced coupling with the ACC. Those authors suggested that there was a greater interplay between internally generated visual information and spontaneous mind-wandering, and a decrease in cognitive control.

Potential Therapeutic Uses of Ayahuasca

Although the full potential of ayahuasca remains unknown, a growing body of evidence accumulated over the last two decades suggests that it may have potential benefits to treat depression. This hypothesis is supported by data on the modulatory capacity of prefrontal 5-HT2A receptors on the amygdala and ACC reported in previous studies (Vollenweider & Kometer 2010). Numerous studies in animals (Aricioglu & Altunbas 2003; Farzin & Mansouri 2006; Fortunato et al., 2009, 2010a, b; Lima et al., 2007; Pic-Taylor et al., 2015; Réus et al., 2010, 2012) and humans (Barbosa Giglio & Dalgalarrondo, 2005; dos Santos, Landeira-Fernandez, Strassman, Motta & Cruz, 2007) have investigated this potential effect of ayahuasca. Several recent studies have evaluated the effects of a single dose of ayahuasca in psychiatric depressive inpatients. Osório et al. (2015) observed a significant reduction in depressive symptoms and anxiolytic effects in six resistant-to-treatment depressive patients during the first week. Those authors suggested that ayahuasca might have an earlier onset of action than traditional antidepressants that have a mean onset of therapeutic action of 2 weeks. In a subsequent study with a larger sample size (n = 17), that same group found significant decreases in depression scale scores, which occurred as soon as 80 minutes after intake up to day 21 post-intake (Sanches et al., 2016). The SPECT analysis revealed increased blood perfusion in brain regions implicated in the regulation of mood and emotional states, as mentioned before.

Recently, Palhano-Fontes et al. (2017) conducted a double-blind placebo-controlled trial (RCT) in treatment-resistant depressive patients to compare a single dosing session of ayahuasca to placebo, and found that the single dosing session showed rapid antidepressant effects. Between-group effect sizes increased from day 1 to 7, and response rates were significantly higher in the ayahuasca group at day 7. Remission rate showed a trend toward significance between groups (36% v. 7%, $p = 0.054$). As discussed above, S1R, which upregulates brain derived neurotrophic factor (BDNF) and nerve growth factor (NGF), has been implicated in depression. The regulation and expression of BDNF and NGF have been recently linked to the pathophysiology and treatment of depression (Otte et al., 2016), data that suggest that DMT-mediated S1R modulation will likely play a key role in efforts to identify future therapies to treat depression and related disorders.

Studies of anxiety symptoms in animal models (Aricioglu & Altunbas, 2003) have found that harmane (another β-carboline) diminishes anxious behaviors in the elevated plus maze (EPM) test; Hilber and Chapillon (2005) reported mixed results for harmaline in that same EPM anxiety test. Pic-Taylor et al. (2015) reported decreases in locomotor and exploratory activities in the open field and EPM tests (similar to fluoxetine). Those authors also observed increased c-fos expression in specific brain areas, confirming that ayahuasca alkaloids affect areas involved in emotional processing.

In humans, Barbosa, Giglio & Dalgalarrondo (2005) reported a decrease in anxiety associated symptoms after the first-time ritual use of ayahuasca among members

of a religious group (Santo Daime) in Brazil. They also observed self-reported behavioral changes, such as increased assertiveness, vivacity, and joy. A case-control study (dos Santos et al., 2007) reported lower scores on panic- and hopelessness-related scales among individuals who took ayahuasca, but no changes in state or trait anxiety.

In recent years, promising findings about the potential effects of ayahuasca on addiction disorders have been reported. Oliveira-Lima et al. (2015) developed a substance use disorder (SUD) model in animals. Those researchers induced hyper-locomotion using ethanol, leading to locomotor sensitization. The results of that study showed that ayahuasca not only inhibited early behaviors associated with the initiation and development of ethanol addiction, but was also effective for reversing the behavioral sensitization associated with chronic ethanol administration.

In humans, effects of ayahuasca on substance use were reported in two case-control studies (Fabregas et al., 2010; Grob et al., 1996). Grob et al. (1996) reported remission of alcohol use in a sample of 15 long-term ayahuasca users compared to 15 matched controls with no prior history of ayahuasca ingestion. Fabregas et al. (2010) reported a reduction in alcohol use and cessation of drug use (except for cannabis) in two groups of jungle and urban-based ayahuasca users compared to non-ayahuasca users, with outcomes maintained at one-year follow-up. Halpern, Sherwood, Passie, Blackwell & Ruttenber (2008) reported remission of drug or alcohol abuse/dependence in a community sample of ayahuasca users (average length of membership, 6.5 years). In another case series (Thomas, Lucas, Capler, Tupper & Martin, 2013), Thomas and colleagues found statistically significant reductions in cocaine use after an ayahuasca-assisted intervention in a sample of members of a First Nations community in Canada who had no prior experience with ayahuasca. Other descriptive studies (Bouso & Riba, 2014; Doering-Silveira et al., 2005a, b; Labate, dos Santos, Strassman, Anderson & Mizumoto, 2014) have presented preliminary evidence suggesting a potentially beneficial role for ayahuasca in the treatment of SUD.

Given the growing body of evidence on the potential therapeutic use of ayahuasca in depression, anxiety and SUD, there is increasing interest in testing whether ayahuasca can be used to treat a broader range of related disorders. In this context, in a recent review (Domínguez-Clavé et al., 2016), our group postulated that ayahuasca could also be valuable in treating other impulse-related disorders, personality disorders, and even trauma.

Psychological Mechanisms Underlying the Therapeutic Effects of Ayahuasca

In recent years, our group has published research suggesting that a psychological mechanism—an increase in mindfulness-related capabilities (e.g., Soler et al., 2016)—could underlie the potential therapeutic effects of ayahuasca. In our first

study, 25 individuals completed the Five Facets Mindfulness Questionnaire (FFMQ) and the Experiences Questionnaire (EQ) before and 24 h after an ayahuasca session. We found significant reductions in two facets of mindfulness, "nonjudging" and "non-reacting." A decrease in nonjudging indicates a reduced tendency to be evaluative and judgmental; that is, the person is less likely to dichotomize experiences into either "good" or "bad." Improvements in nonreacting indicate decreased reactivity to private experiences such as thoughts and feelings, regardless of whether those are pleasant or unpleasant.

The study also found significant increases in "decentering" as measured by the EQ. Decentering is considered a product of mindfulness practice. This concept has been defined as "the ability to observe one's thoughts and feelings in a detached manner, as temporary events in the mind, as neither necessarily true nor reflections of the self" (Safran & Segal, 1990). Previous reports (Bergomi, Stroehle, Michalak, Funke, & Berking, 2013; Soler et al., 2014) have found that meditation practice is beneficial for all three of the aforementioned facets (i.e., nonjudging, nonreactivity, and decentering).

However, improvement in decentering can be achieved by therapeutic interventions other than mindfulness practice, such as Acceptance and Commitment Therapy (ACT) (Hayes, Strosahl & Wilson, 1999) and Metacognitive-Based Therapy (MBT, Wells, 2009). These therapies focus on decentering, which plays a key role in contributing to their beneficial effects (Moritz et al. 2011; Van der Heiden, Muris & van der Molen, 2012; Wells et al., 2010). Franquesa et al. (2018) compared ayahuasca-naive subjects ($n = 41$) to experienced users ($n = 81$), finding that ayahuasca users scored higher on decentering measures than nonusers, even when the most and least experienced users were compared. By improving decentering, individuals gain mastery over their thoughts and emotions, minimizing or even eliminating the tendency to identify with them (Shapiro, Carlson, Astin & Freedman, 2006).

Studies have found that the capacity to "decenter" may be protective against suicidal ideation and that an individual's decentering ability is predictive of the intensity of depressive symptoms at a 6-month follow-up (Bieling et al. 2012; Hargus, Crane, Barnhofer & Williams, 2010). In this regard, the efficacy of cognitive behavior therapy (CBT) in the treatment of depression may rely on increasing this decentering capacity (Teasdale, Segal & Williams, 1995). In the context of these findings, studies have found that improving an individual's decentering capacity could directly improve depression (Bieling et al., 2012; Fresco et al., 2007a, Fresco, Segal, Buis & Kennedy, 2007b; Gecht et al. 2014; Hargus et al., 2010; Teasdale et al., 2002), generalized anxiety disorder (Hayes-Skelton, Calloway, Roemer, & Orsillo, 2015; Hoge et al., 2015), social anxiety (Hayes-Skelton & Graham, 2013), eating disorders, SUD (Shapiro, et al. 2006), and borderline personality disorders (BPD) (Soler et al., 2014). In impulsive-related disorders (such as drug abuse or BPD), an increase in the decentering capacity may diminish mood-dependent behavior by interrupting recurring maladaptive habits (Shapiro et al., 2006).

Regarding mindfulness-related capacities, ayahuasca intake seems to induce a pattern of change similar to that produced by mindfulness practice. In fact, the two

main facets that improve after ayahuasca use—nonjudging and nonreacting to inner experience (Soler et al., 2016)—make up the acceptance-measuring components of the FFMQ (Baer, Smith, Hopkins, Krietemeyer & Toney, 2006).

A recently published neuroimaging study examined the effects of ayahuasca in a sample of healthy volunteers with prior experience using the substance (Sampedro et al., 2017). That study found increases in the nonjudging subscale and found that post-acute neural changes predicted sustained elevations on the nonjudging subscale at 2 months post-intake. An even more recent study (Soler et al., 2018), which compared mindfulness training to ayahuasca, found that ayahuasca induced increases in the nonjudging scale that were comparable to those of mindfulness. Based on these studies, it appears that only a few ayahuasca sessions may be as effective at improving acceptance as costly interventions. Improving this capacity allows a more detached and less judgmental stance towards potentially distressing thoughts and emotions.

In a recent observational study (Domínguez-Clavé et al., 2019), our group examined the effects of ayahuasca in a sample of volunteers participating in an ayahuasca ceremony. Of the 45 participants, 12 exhibited BPD-like traits and were allocated to a subgroup. After comparing both samples (non-BPD-like and BPD-like), we found that the BPD-trait subgroup showed significant pre-post difference in the emotion regulation (ER) subscales of Difficulties in Emotion Regulation Scale (DERS) *Lack of Control* and *Emotional Interference*. The non-BPD traits subgroup showed significant pre-post differences for those same two subscales, as well as for DERS *Emotional Non-acceptance*. The non-BPD subgroup also showed significant effects on most FFMQ subscales (*Observing*, A*cting with Awareness*, *Nonjudging* and *Nonreacting*) and in decentering (EQ).

That study was the first to examine the effects of ayahuasca on ER and the first to use a subsample of individuals with BPD-like traits. Those findings led us to believe that ayahuasca therapy could be of value in clinical populations affected by emotion dysregulation. Moreover, an exploratory study conducted by members of our team in 45 volunteers found that ayahuasca use positively influenced measures of self-compassion and self-criticism assessed 24 h before and after ayahuasca intake.

An improved understanding of this connection between ayahuasca-induced experience and mindfulness techniques could help to better characterize the therapeutic effects of ayahuasca. If ayahuasca enhances ER—or more specifically, acceptance or self-compassion—it could conceivably also exert a therapeutic effect on individuals with mental disorders by targeting ER capacities. Future studies should address the benefits of combining ayahuasca with mindfulness-related practices to provide a more focused approach to better treat specific disorders. The influence of ayahuasca on these psychological mechanisms suggests its potential to also treat trauma-related conditions and other disorders such as BPD (Bohus Dyer, Priebe, Krueger, & Steil, 2011; Bohus et al., 2013; Harner & Burgess, 2011; Harner, Budescu, Gillihan, Riley & Foa, 2015), obsessive-compulsive disorder, and phobias, in a structured, safe, and comfortable setting.

Metabolic and Connectivity Changes and Mindfulness-Related Capacities

The term "after-glow" designates the positive post-acute effects of psychedelic drugs characterized by elevated mood and openness (Pahnke, Kurland, Unger, Savage & Grof, 1970). Sampedro et al. (2017) has investigated the post-acute neurometabolic and connectivity changes induced by ayahuasca. Neuroimaging techniques (1H-magnetic resonance spectroscopy and functional connectivity) revealed post-acute reductions in glutamate+glutamine (Glx), creatine, and N-acetylaspartate+N-acetylaspartylglutamate (NAA-NAAG) in the PCC. Additionally, reductions in Glx correlated with increases in the FFMQ non-judging subscale and were maintained after 2 months. The inverse correlation between Cr and NAA-NAAG and the scores on the Hallucinogen Rating Scale (HRS)-cognition subscale suggested a relationship between the intensity of acute effects and subsequent neurometabolic reductions. Moreover, connectivity between the ACC and PCC and between the ACC and limbic structures in the right MTL increased. The results suggest that cross-talk lingers beyond the acute stage and contributes to the "after-glow" that is reflected in enhanced mindfulness capacities. These findings confirm previous data regarding the capacity of ayahuasca to enhance mindfulness capacities, including increased "decentering" and decreased judgmental and reactive attitudes (Soler et al., 2016).

Interestingly, in a study published in 2014 (Soler et al., 2014), the authors found that ayahuasca can even increase mindfulness and self-compassion capabilities in individuals who already have high baseline capabilities. In that study, ayahuasca users had higher post-acute scores than meditators. Additionally, Sampedro and colleagues' study showed increased DMN-TPN connectivity correlated with reduced judgmental processing, inner reactivity, and increased self-kindness, providing a neurobiological basis for these modifications. These findings also points to a potential biological basis for therapeutic benefits. Conventional mindfulness training also increases this cross-talk between networks (Doll et al., 2015).

The potential of ayahuasca to influence brain dynamics at multiple levels suggests its potential to treat disorders that are highly refractory to other therapeutic interventions. Its combined effect on the psychological and neural spheres may be particularly well-suited to treating addiction disorders, where high impulsivity and self-centeredness coexist with alterations in brain function and structure.

B. Caapi, β-carbolines, and Neurogenesis

Given that β-carbolines, unlike DMT, are present in all ayahuasca brews, Morales-García et al. (2017) recently evaluated these metabolites to investigate the capacity of harmine, THH, harmaline, and harmol to induce neurogenesis in vitro using neural progenitor cells from adult mice. In the adult brain of mammals, neurogenesis—

the process of generating functional neurons from progenitor cells—is limited to specific brain regions such as the subventricular zone (SVZ) of the lateral ventricle and the subgranular zone of the dentate gyrus of the hippocampus (SGZ). Although this system in the adult brain is considered relatively robust, the number of neural stem cells (NSC) progressively decreases with age and in neurodegenerative diseases.

Impaired adult neurogenesis in neurodegenerative diseases, in addition to losing existing neurons, involves brain's endogenous loss of capacity for cell renewal and therefore the impairment and/or loss of putative function of these new neurons. Morales-García and colleagues showed that *B. caapi* alkaloids stimulate the proliferation and migration of progenitor cells and promote differentiation (predominantly) into neurons. These alkaloids increase the number and size of primary neurospheres (neural stem cell-enriched spheres), induce the loss of their undifferentiated state, and promote subsequent cell migration and differentiation into a neuronal phenotype (as indicated by the positive expression of the neuronal markers β-III-tubulin and MAP 2), as well as astrocytes. Taken together, these three effects indicate that β-carbolines have the capacity to regulate the expansion and fate of stem cell populations. The largest effects on migration have been observed for harmaline and THH. Increased migration capacity is relevant in certain conditions such as brain injury, where stem cell niches are far from the damaged area.

Neural stem cells can differentiate into neurons, astrocytes, and oligodendrocytes. In the aforementioned study, the observed increase in Tuj-1 and MAP-2 protein expression indicated differentiation, mainly towards a neuronal phenotype (Fig. 1.1). In the SVZ, both proteins were equally expressed after treatment with each of the four compounds (harmine, THH, harmaline, and harmol). However, in the SGZ, harmine administration did not influence Tuj-1 levels, a marker of immature neurons, but did significantly increase the expression of MAP-2, suggesting that harmine has a larger impact on neuronal maturation. Importantly, the magnitude of the neurogenic effects was similar for the four alkaloids, whose versatility is of interest given that, in pathological conditions, these compounds could optimize the replacement of neurons by simultaneously acting on various processes.

A likely possible explanation for the observed effects of β-carbolines on neurogenesis is the increase in monoamine levels caused by MAO inhibition. However, other studies reported neurogenesis as independent of elevated serotonin levels. A recent study (Song et al., 2016) found that serotonin depletion appears to promote, rather than decrease, hippocampal neurogenesis. Another group of researchers (Dakic et al., 2016) found that harmine—but not the MAO inhibitor pargyline—stimulated the proliferation of human neural progenitor cells in vitro. In that case, the effects of harmine were mediated through inhibition of the DYRK1A kinase rather than through MAO inhibition. These results suggest that β-carbolines regulate stem cell fate via DYRK1A or other alternative mechanisms.

The association between neurogenesis and anti-depressant activity is well-documented. Clinically effective antidepressants have been reported to stimulate this process, regardless of their specific chemical structure and mechanism of action.

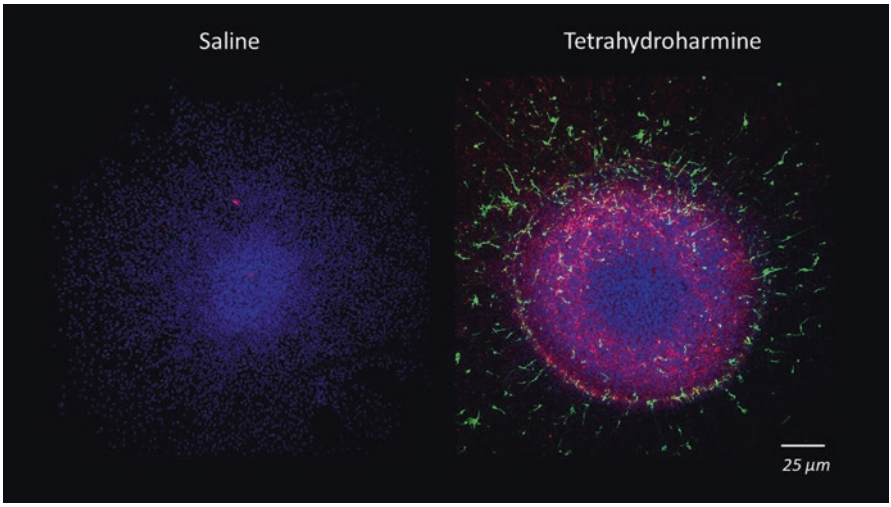

Fig. 1.1 Ayahuasca β-carboline alkaloids induce neurogenesis in vitro, promoting stem cell differentiation towards a neuronal phenotype. Rodent neural stem cells were isolated from one of the most important adult neurogenic niches, the subgranular zone of the hippocampal dentate gyrus, and cultured as free-floating neurospheres in the presence of tetrahydroharmine (THH). After 7 days, neurospheres were adhered on coated coverslips and allowed to differentiate for 3 days in the presence of THH
The figure shows triple confocal immunofluorescence images showing the expression of the neuronal markers β-III-Tubulin (TuJ-1 clone, green, early neurogenesis) and microtubule-associated protein 2 (MAP-2, red, mature neurons) in control (left) and treated (right) neurospheres. DAPI was used for nuclear staining. Scale bar = 25 μm
The left half of the figure shows results after saline (no neurogenesis)
The right half of the figure shows results after THH (evidence of early neurogenesis and presence of mature neurons)

However, it is still unclear if enhanced hippocampal neurogenesis reduces depression-like behavior (Dean & Keshavan, 2017; Hill, Sahay & Hen, 2015).

More research is needed to determine the true magnitude of the therapeutic potential of ayahuasca in mental health and to better identify the mechanisms that mediate the action of *B. caapi* alkaloids.

Conclusions

Recent years have witnessed an explosion in the number of studies on the effects of psychedelics. In this chapter, we have described the latest research on ayahuasca. Highly promising research results showing that (a) DMT can protect neurons from hypoxia; (b) the serotonin-2A receptor mediates the visual effects of ayahuasca; and (c) ayahuasca intake can diminish pathological patterns of thought and behavior,

such as those observed in depression and addiction. Here, we have discussed how these modified patterns result from the enhancement of metacognitive capacities that allow individuals to observe their own thoughts and emotions in a healthier and less judgmental manner.

The recent discoveries described in this chapter about new mechanisms of action and psychological capacities of ayahuasca, such as its impact on facets of mindfulness, decentering, and emotional regulation, open new horizons in terms of potential therapeutic interventions for mental disorders. Given the important effects of ayahuasca on many regions of the brain—as shown by neuroimaging studies and neurophysiologic techniques—the optimal approach may be to combine ayahuasca with psychological interventions, as a combined treatment may yield better treatment outcomes. This chapter has also described the neural correlates underlying these psychological benefits, which have been identified through a combination of state-of-the-art neuroimaging techniques. Finally, at the cellular level, we have described how the β-carbolines present in ayahuasca stimulate the formation of new neurons in the adult mammal brain.

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