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Effects of ayahuasca on fear and anxiety: cross-talk between 5HT1A and 5HT2A receptors

Lorena Terene Lopes Guerra[1], Rafael Guimarães dos Santos[1,2], and Jaime Eduardo Cecilio Hallak[1,2]

Ayahuasca is a hallucinogenic substance currently being investigated for the treatment of mood, anxiety, and trauma-related disorders. Evidence from animal and human studies suggest that the effects of ayahuasca involve modulation of neural substrates relevant for emotional processing, especially in regions rich in serotonergic receptors. Moreover, preclinical studies also show that ayahuasca has specific effects on fear-related memories. The serotonergic system has been classically associated to anxiety and fear responses, with selective serotonin reuptake inhibitors being first-class medication to treat mood, anxiety, and stress-related disorders. Here we review currently available data regarding ayahuasca (and its main components) behavioral and functional effects on anxiety and fear-related responses through its modulation of serotoninergic signaling.

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Introduction

Ayahuasca (AYA) is a hallucinogenic beverage traditionally consumed by indigenous groups from Northwestern Amazon and, more recently, by syncretic religious groups present worldwide. The main psychoactive compound in AYA is N,N-dimethyltryptamine (DMT), present in the leaves of *Psychotria viridis*, but the preparation of AYA also involves the *Banisteriopsis caapi* vine, rich in β-carbolines (1). The β-carbolines act as antagonists on digestive system monoamine oxidase enzymes that, otherwise, would degrade DMT before it could reach the central nervous system (2). Harmine, tetrahydroharmine, and harmaline are the most relevant β-carbolines in AYA, which have their own pharmacological properties, adding another layer of complexity to the mechanisms of action of AYA (3).

AYA can be defined as a classic hallucinogen, since it has agonistic effects in different serotonergic receptors, especially the 2A subtype (5HT2A receptor) (4). The subjective and hallucinogenic effects of AYA seem to result from its agonism at 5HT2A receptors; however, it can also act on different receptor subtypes, with the 1A receptor (5HT1A) being of special interest for the discussion proposed by this review (5, 6). The effects of AYA on serotonergic pathways mostly rely on DMT action, since β-carbolines present little to no affinity for most serotoninergic receptors, except for a modest affinity for the 5HT2A receptor (3, 5).

Similarly to what have been happening to other psychedelic substances, AYA properties have been investigated as treatment for numerous psychiatric disorders, such as depression, anxiety, and substance use disorder (7–11). Additionally, preclinical studies have suggested a possible action of AYA on fear processing circuits, which could support possible mechanism for therapeutic effects on anxiety and posttraumatic stress disorder (PTSD) (12, 13). A few observational studies and case reports have already been published about therapeutic effects of AYA on trauma processing and treatment of PTSD (14, 15), with promising results. Nonetheless, until now, clinical trials performed in controlled settings are lacking.

Apart from serotonin receptors, AYA also has effects on glutamatergic, dopaminergic, and endocannabinoid systems (16–18). It is possible that DMT acts as an agonist of *sigma-1* receptors (19), which was already suggested as a possible mechanism for AYA effects on fear processing (20). Moreover, AYA intake can alter neuroendocrine responses as well (21). These complex interactions, however, are beyond the scope of this review. Here, we aimed to concatenate and discuss data regarding AYA effects on fear and anxiety and how it can be associated with its actions on serotonin (5HT) receptors.

Fear Behavior and Anxiety

Fear is an evolutive preserved behavior that acts as a defense mechanism and is usually triggered by threatening and dangerous stimuli. Some stimuli can naturally elicit a defensive behavior, while others can be learned and associated to lifelong responses. This behavioral plasticity is crucial for adaptation to an environment that continuously challenges individuals with new contexts (22). Anxiety, on the other hand, represents a state of increased arousal and vigilance even in the absence of an imminent threat, and it can also elicit behavioral defensive responses (23).

Impairments on appropriate fear and anxiety responses are the cause of a variety of psychiatric disorders, such as PTSD, generalized anxiety and panic disorders (24). Efforts to develop better treatment options for patients suffering from these disorders demand the development of tests and paradigms that can assess the behavioral and neural alterations underlying the symptoms.

Paradigms for Assessing Fear and Anxiety Responses

The more frequently employed paradigms to assess fear and anxiety responses in preclinical studies usually are rooted on inherent behavioral characteristics of the animals or on associative learning of conditioned responses to naturally aversive stimuli.

In the first category, the animal behavior is affected by an approach-avoidance conflict between the inherent tendency for the animal to explore the new environment versus fear-driven behaviors. The elevated plus-maze (EPM) and the open field test (OFT) are two of the most famous tasks based on this premise. Animals expressing increased anxiety-like behavior spend more time on the closed arms (EPM) or in the edges of the field (OFT), respectively. Treatment with anxiolytic drugs increase entrances and time spend on the open arms for the EPM, as well as time spent in the center of the arena for the OFT (25, 26).

On the second category, the classical or Pavlovian conditioning is the most widely employed protocol to study fear behavior and memories.

[1]Departamento de Neurociências e Ciências do Comportamento, Universidade de São Paulo, Ribeirão Preto 14015-010, Brazil; [2]National Institute of Science and Technology Translational Medicine (INCT-TM) 14015-010, Brazil

Corresponding Author: Prof. Rafael Guimarães dos Santos, Departamento de Neurociências e Ciências do Comportamento, Faculdade de Medicina de Ribeirão Preto, Universidade de São Paulo, Hospital das Clínicas, Terceiro Andar, Av. Bandeirantes, 3900, Ribeirão Preto, São Paulo, Brazil. Phone: +551636350713. E-mail: banisteria@gmail.com

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Through this paradigm, a stimulus once neutral, that is, that does not elicit a behavioral response, is paired to a stimulus that naturally evokes a fear response. Once the animal is trained through simultaneous presentations of the latter (that is called the unconditioned stimulus or US) together with the former (which will be called the conditioned stimulus or CS), an associative memory is acquired and the CS alone is able to evoke the behavioral response (27, 28). Alterations in US intensity and CS characteristics can result in memories with different characteristics, like duration, intensity of evoked behavioral response and generalization (22). The two more frequently employed fear conditioning paradigms are the contextual fear conditioning (CFC) and the tone fear conditioning (TFC). Both apply electric shocks at the animal's paw as the US, but the first uses the whole context where the animal is trained as the CS, and the latter uses a specific sound as the CS, and the animal is tested being exposed to the same sound but in a different context from training (29).

Fear conditioning protocols have been widely employed by preclinical researchers as a tool to understand memory formation as well as how they can be altered or forgotten. Repeated re-exposure to the CS is the base for reconsolidation and extinction protocols (30). If elucidating the fear memory formation is relevant, understanding how already established responses can be altered can be even more valuable to contribute for treating disorders like PTSD (31).

In humans, the behavioral and subjective consequences of fear and anxiety are frequently assessed using specifically developed psychometric instruments. However, there are many tasks as well that can be employed, being especially useful when accessing neural alterations underlying the behavioral responses through neuroimaging techniques.

Social cognition tasks frequently employ emotional relevant stimuli. During tasks involving the recognition of emotions in facial expressions (REFE), subjects are presented to static or dynamic images of facial expressions and asked to recognize pictured emotion. There are many variations in these tasks, but several are based on Ekman's theory of basic universal emotions (32). Performance in these tasks seems to be altered by numerous conditions, especially when responding to negative valence emotions, like fear (33–35). Another task example is the Simulation of Public Speaking Test (SPST), an anxiety-induced task where individuals are asked to elaborate a speech on a random matter and present it in front of camera, mimicking a public speak situation (36).

Neural Substrates Underlying Fear and Anxiety Responses

Multiple brain regions are involved on processing of emotionally relevant stimuli, but a significant part of the available data produced in the last decades focuses on understanding cortical-limbic circuits dynamics. In this section, we will focus on prefrontal cortex (PFC), amygdala (AMY), and hippocampus (HPP) influence on fear and anxiety processing. Later (Section 2.3), raphe nuclei innervations to these structures will also be discussed.

Prefrontal Cortex. The PFC is involved in numerous executive processes. It receives and projects to structures relevant to emotional, cognitive, sensory, and motor functioning, resulting in a central integrative role for behavioral control and flexibility, highly influenced by external cues and internal contingencies (37). Although there is an ongoing debate regarding the homologies between rodent and primate composition of the PFC, the medial PFC (mPFC) from rodents holds similarities in the modulation exerted by human dorsolateral, medial and cingulate cortices over memory, emotional regulation and response control, among other functions (38).

The rodent mPFC includes two main subdivisions, the prelimbic cortex (PL), that together with the anterior cingulate cortex constitutes the dorsal mPFC, and the infralimbic cortex (IL), more ventrally located. Despite being closely located and intimately interconnected, these two regions have different projecting profiles (37, 39). The PL have more efferent connections with the basolateral nucleus of the AMY (BLA), and dorsal and median raphe nuclei, while the IL innervates numerous AMY nuclei, but especially the central AMY nucleus (CeA), and the lateral septum (39).

The PL projections, although not necessary for fear conditioning acquisition, are needed for the consolidation of the associative fear memory (40). The PL is also relevant for freezing expression after TFC, since CS-modulated disinhibition of PL principal neurons (PNs) projections to the BLA is relevant for fear expression during test (41). The IL activity does not influence fear acquisition or consolidation; however, it is essential for fear extinction retention, suggesting a role on behavioral flexibility (42). Optogenetically silencing IL PNs during extinction learning does not interfere with freezing reduction within session, but impaired extinction recall. However, silencing the PNs during extinction test does not impair extinction recall, indicating that proper IL activation is necessary for consolidation of the extinction memory (43).

The mPFC activity exerts a top-down modulation of subcortical structures relevant for emotional regulation (37). Consistent with that, data from clinical and preclinical studies suggest that increased anxiety responses are linked to a hypoactivation of this region, which can also result in impaired cognitive flexibility (44–46). In mice, synchrony between mPFC and BLA activity is related to discrimination of safety contexts during fear learning and anxiety protocols (47). Similarly, when compared with healthy controls, patients with generalized anxiety disorder had reduced ventromedial PFC activation when processing safety signals (48).

Regarding PL and IL, their precise role on modulation of anxiety responses is less well defined, with contrasting results on the literature, that may result from projections' functional heterogeneity (49).

Amygdala. The AMY is a subcortical structure comprising different nuclei and located in the medial temporal lobe. It receives projections from cortical and subcortical structures, essentially acting as an information processing hub that translate sensory inputs to other areas relevant to behavioral control and emotional processing, such as the PFC and HPP (50, 51).

During fear conditioning, the CS and US association depends on an intricate temporal balance of the different AMY nuclei activation (22). The lateral portion of the AMY is the input region for sensory information, and it is also where the CS and US stimuli representations are associated. However, the communication with other AMY nuclei depends on glutamatergic projections leaving from the basal AMY. Since both regions are intimately interconnected, they are often referred as the basolateral AMY (BLA) (52). If the BLA is the main input center, the central AMY (CeA) is the output, projecting to structures relevant for fear expression, such as the hypothalamus and the periaqueductal gray (53). The BLA PNs innervate de CeA directly, but also regulate its activity indirectly through projections to the intercalated cells (ITC), a GABAergic cell mass, that also innervates the CeA (54). AMY activity is necessary for both CFC and TFC, but on the former, the context representation relies on dorsal HPP activity which then indirectly communicates with the AMY through ventral HPP projections (29, 55).

Altered activity in different AMY nuclei is associated to anxiety responses. Inside the AMY, activation of projections from the BLA to CeA have an anxiolytic effect, while selective optogenetic inhibition of these neurons result in an increase of anxiety-like behavior in mice (56). Functional connectivity between these two subregions is also impaired in patients with generalized anxiety disorder (57). When exposed to emotional relevant stimuli, patients with anxiety and trauma-related disorders tend to present increased AMY response (58).

Hippocampus. The HPP is located in the temporal lobe and implicated in multiple cognitive, memory and emotional processing functions. This structure can be functionally differentiated into two distinct areas, the ventral HPP and the dorsal HPP (59).

The dorsal HPP functioning is associated to cognitive performance and is responsible for encoding the representation of the context during CFC, hence why this task is described as HPP-dependent. Lesions on the dorsal HPP impair CFC expression without altering TFC (60).

Additionally, HPP is one of the few structures where new neurons can be born in adult brains (61), although there is an ongoing debate whether this property is present in humans (61, 62). Impaired neurogenesis seems to be related to symptomatology of multiple psychiatric disorders, like depression and PTSD (63).

However, this hippocampal region does not directly project to the AMY and the integrations of context representation to sensory inputs to AMY

depends on ventral HPP projections (64). Added to its role on CFC acquisition, dorsal HPP also is relevant for fear memory recall and extinction (65, 66).

The ventral HPP, on the other hand, is more associated to emotional processing, being the only HPP region projecting directly to AMY (64). Additionally, the ventral HPP also seem to be relevant for expression of anxiety responses. Anxiogenic environments increase synchronization of mPFC and ventral HPP, the same not being reported for the dorsal HPP (67). Additionally, lesions on the ventral HPP lead to decrease in anxiety-like responses in the EPM (68).

In humans, PTSD is associated with decreased HPP volume and impaired HPP activation in women performing a verbal declarative memory task (69), and it is also associated with reduced HPP activation to trauma-related stimuli (70). In patients with generalized anxiety disorder, the anterior HPP (analog to the ventral HPP in rodents) had decreased activation to repeated exposure to threat cues when compared with healthy controls (71).

Serotonin Effects on Fear and Anxiety Responses

Studies on human serotonin receptors are intimately linked to hallucinogenic compounds. In 1953, Gaddum reported lysergic acid diethylamide (LSD) antagonistic effect over 5-HT responses elicited in vitro (72, 73) and, since then, seven serotonin receptor classes have been described, mostly represented by G-protein coupled receptors (74). Although hallucinogenic compounds can interact with different 5HT receptor classes, most of the available data focus on the 5HT2 and 5HT1 subtypes, specifically the 2A and 1A subtypes (75).

The 5HT2A subtype is $G_{q/11}$-coupled and abundantly expressed in cortical areas, especially on layer V dendrites of PNs, which are densely innervated by 5HT axons (76). Their activation mostly produces increased membrane excitability through a slow membrane depolarization and inhibition of calcium activated after-hyperpolarization currents (77).

The 5HT1A receptors, on the other hand, are presynaptically expressed on 5HT neurons of the raphe nuclei where they act as autoreceptors and regulate 5HT release (78). However, they are also widely distributed through substrates relevant to memory and emotional processing, such as the HPP, cingulate and entorhinal cortices and AMY, where they are postsynaptically expressed (79, 80). These receptors are coupled to the G_i protein, and their activation induces membrane hyperpolarization through increase in rectifying potassium currents and inactivation of calcium channels (74, 77).

The seemingly opposing effects of 5HT2A and 1A receptors on membrane potential may appear contradictory as they are often co-expressed on cortical PNs (81), but these differences are relevant for stimuli processing. The hyperpolarizing action of 5HT1A alters the sensibility to input-generated excitability, restraining firing frequency, while the inhibition of after-hyperpolarization induced by 5HT2A activation increases excitability, modulating neuronal gain (77). Apart from PNs, these receptors can be expressed on cortical GABAergic interneurons (INs) as well, adding another layer of complexity to serotonergic control over cortical excitatory/inhibitory balance (76, 81).

Through the 70s and 80s many studies explored how 5HT affected punishment conditioned behaviors. At the time, 5HT signaling pathways were thought to regulate these behaviors and promote punishment-induced response suppression. Although further evidence elucidated that this relationship is not as straightforward as initially thought, 5HT role on fear and anxiety neurobiology is still undeniable, with selective 5HT reuptake inhibitors (SSRIs) being the first line of treatment for many stress and anxiety disorders (24).

The theory formulated by Deakins and Graeff proposes that distinct fear and anxiety behavioral responses are controlled by specific 5HT pathways arising from the raphe nuclei. The dorsal raphe (DRN) periventricular tract is responsible to react to acute US exposure, controlling flight or fight responses, and mostly modulating the periaqueductal gray activity. The DRN forebrain bundle tract (DRD/DRC) is activated by acute exposure to CS and controls avoidance behaviors through projections to structures such as the AMY, ventral HPP and PFC. And the median raphe forebrain bundle tract (DRI/MnR) responds to chronic US and/or CS exposure, being responsible to promote resilience or tolerance to chronic stress, projecting to the dorsal HPP and PL and IL cortices, acting mostly though postsynaptic 5HT1A activation (82, 83).

Knock-out mice for the 5HT2A receptor present decreased anxiety-like behaviors, but have normal CFC and TFC, and the reestablishment of 5HT2A signaling in cortical neurons normalized the anxiety-like responses (84). In the BLA, activation of 5HT projections of DRN increases anxiety-like responses through 5HT2A activation (85).

Pretreatment with the 5HT2A agonist TCB-2 or antagonist MDL 11,939 before acquisition and retrieval of conditioned fear memory did not interfere with freezing expression of male mice, while TCB-2 administration posttraining enhanced freezing on CFC and TFC tests. As for the extinction learning, 5HT2A activation is not essential, but facilitates the process (86). Altogether, these data suggest a role for the 5HT2A receptor on plasticity mechanisms altering memory traces and behavioral responses, but that role is limited to already acquired memories and does not seem to influence the establishment of new associations.

Activation of postsynaptic 5HT1A receptors, on the other hand, seems to decrease anxiety and stress responses. Systemic or intrahippocampal treatment with 5HT1A agonist 8-OH-DPAT before CFC impairs fear memory retrieval, without significantly altering TFC memory retrieval. The impairments were not observed when treatment was administered after training. Additionally, WAY 100635, a 5HT1A antagonist, was not able to produce memory alterations when administered alone, but prevented retrieval impairments when combined with 8-OH-DPAT. Opposed to the outcomes observed after 5HT2A manipulation, 5HT1A receptors seem to be relevant for memory acquisition, especially of HPP-dependent memories, like the CFC (87).

Serotonin Receptors' Role on Psychedelic Effects

The behavioral and mental alterations resulting from psychedelic administration are frequently associated to its agonism at 5HT2A receptors. In humans, ketanserin, a 5HT2A/2C antagonist, can be used to reduce subjective effects induced by LSD (100 or 200 μg) (88, 89). Pretreatment with ketanserin also prevents the psilocybin-induced (215 μg/kg) increase in positive affect and the decrease on recognition of negative facial expressions (90). For DMT (0.7 mg/kg, i.m.), pretreatment with cyproheptadine, another 5HT2A/2C antagonist, did not interfere with subjective effects (91). On the other hand, pretreatment with pindolol, a 5HT1A/β-adrenergic receptors antagonist, intensified DMT (0.1 mg/kg, i.v.) subjective reactions, suggesting an attenuation response of 5HT1A receptors activation on DMT effects. The enhancement of subjective effects caused by pindolol could be a result of increased 5HT2A signaling after 5HT1A blockade (5).

Regarding AYA, pretreatment with ketanserin altered the neurophysiological oscillatory patterns induced by AYA (dose adjusted to contain 0.75 mg/kg of DMT) intake and blocked visual effects through blocking AYA-induced decrease in alpha oscillations (6).

Although the available literature mostly attributes the subjective effects of psychedelics to agonism at the 5HT2A receptor, some evidence points out that not everything can be explained by it. In healthy volunteers, pretreatment with ketanserin did not prevent the reduction in attentional tracking ability caused by psilocybin (215 μg/kg), suggesting a role for 5HT1A receptors (92). Combined administration of buspirone, 5HT1A agonist, and psilocybin (170 μg/kg) reduced the acute subjective effects of psilocybin (93). In chronically stressed mice, treatment with ketanserin did not prevent the antidepressant effects of a single dose of psilocybin (1 mg/kg, i.p.) (94).

Preclinical Evidence for Ayahuasca' Effects on Fear and Anxiety-like Responses

Animal studies evaluating the effects of AYA administration are trying to decode how this substance can interfere with behavioral, functional and structural parameters of fear and anxiety-like responses, and how this could be linked to the possible therapeutic effects (Table 1).

A single oral administration of AYA (containing 9 mg/kg of DMT) to female rats decreased locomotion on the OFT and EPM, which could be an indication of an anxiogenic effect, whilst it also decreased immobility on forced swim test (FST), an indication of antidepressant effect. The

Table 1. Fear and anxiety-like responses from preclinical studies

	Training	Testing	Reconsolidation	Extinction
Fear memory tests				
AYA	–	Chronic pretreatment with AYA (120 mg/kg) increased freezing at CFC and TFC (99).	AYA treatment (60 mg/kg) pretreatment before or after reconsolidation session decreases fear expression on CFC test (12).	Single AYA (0.3 mg/kg of DMT) dose reduces freezing during CFC extinction training, but not test. However, two treatment paired extinction sessions decrease freezing during test (13). Single AYA dose (60 mg/kg) before retrieval, facilitates CFC extinction learning one day after (12).
DMT	Acute treatment with DMT (10 mg/kg) increased freezing during TFC (96). Chronic treatment with DMT (1 mg/kg) did not affect behavior during CFC and TFC training (100).	Acute treatment with DMT (10 mg/kg) before training did not alter fear response during TFC test (96). Chronic treatment with DMT (1 mg/kg) did not affect behavior during CFC and TFC test (100).	–	DMT acute (10 mg/kg) or chronic (1 mg/kg) treatment facilitated TFC, but not CFC, extinction (96, 100).
β-carbolines	Pre-training harmine (10 mg/kg) treatment did not altered aversive avoidance learning during PMDAT training (102).	Pre-training treatment with harmaline (1 mg/kg) impaired fear response at the step-down passive avoidance task (101). Pre-training harmine (10 mg/kg) treatment impaired fear response at CFC, but not TFC (102). Pre-training harmine (10 mg/kg) treatment impaired aversive-avoidance during PMDAT test (102).	–	–
Anxiety test				
AYA	Acute oral AYA dose (9 mg/kg of DMT) decreased locomotion on OFT and EPM (95). Acute oral AYA treatment (0.1, 0.3 of DMT) had no effect on time in the open arms and closed arm entries, but the higher AYA dose (1.0 mg/kg of DMT) increased closed arm entries and general exploratory behavior (13). Oral single dose of AYA (60 mg/kg) did not alter open arm and closed arm entries, and did not alter locomotion (12).			
DMT	One DMT dose (10 mg/kg, i.p.) reduced exploration in the OFT and open arms time and entries on EPM (96).			
β-carbolines	Acute harmine (5, 10, 15 mg/kg, i.p.) treatment did not alter behavioral expression on the OFT (98).			

AYA: Ayahuasca; CFC: Contextual fear conditioning; DMT: N,N-dimethyltryptamine; EPM: Elevated plus-maze; OFT: Open field test; PMDAT: Plus-maze discriminative avoidance task; TFC: Tone fear conditioning; –: Unavailable data.

treatment also induced an increase in *c-fos* expressing neurons in the DRN, posterior BLA and HPP (95). Male rats treated with one dose of DMT (10 mg/kg, i.p.) also presented reduced exploratory and increased anxiety-like behaviors, while three doses were able to induce antidepressant effects on the FST (96). Psylocibin, another 5HT2A psychedelic agonist, also increases anxiety-like responses when administered 15 min prior to the OFT, but promotes anxiolytic effects when animals are tested 4 h after the administration (3 mg/kg, i.p.) (97).

Interestingly, acute treatment with harmine (10 or 15 mg/kg, i.p.) also induced the decrease in depressive-like responses on FST, without altering exploratory behaviors. Additionally, animals treated with the higher dose of harmine also presented increased hippocampal brain-derived neurotrophic factor (BDNF) expression (98).

Further comprehending how AYA can affect fear memory processing might help elucidate how this substance could be useful for treating disorders such as PTSD. Most preclinical studies on this theme focus on how AYA treatment could alter an already established fear memory, which makes sense when considered from a translational point of view. Nevertheless, the results elicited by treatment with AYA and its constituent compounds prior to fear memory formation or during reconsolidation and extinction of already established memories seem to differently affect behavioral responses.

Rats chronically treated with AYA (120 mg/kg, oral) for 30 days and later submitted to CFC and TFC presented enhanced freezing behavior during the test. On TFC test, freezing was increased even before the CS presentation. Treatment with higher doses (240 and 480 mg/kg) did not alter behavioral expression (99). DMT (10 mg/kg, i.p.) also seems to influence freezing behavior when administered 1 h prior to TFC, increasing this behavior during training, but not during test (96). Chronic treatment with smaller doses of DMT (1 mg/kg, i.p.) before the conditioning protocol, on the other hand, does not increase freezing behavior on CFC and TFC tests (100).

β-carbolines, on the other hand, seem to present an amnesic effect when administered to animals prior to fear memory tasks. Harmaline (1 mg/kg, i.p.) injected to mice 5 min before a step-down passive avoidance task training prevented increased latency to step down 24 h later during the retention test (101). Harmine administered (10 mg/kg, i.p.) to rats 1 h before CFC and TFC conditioning decreased freezing behavior when animals were tested for CFC 24 h later but did not affect freezing on the TFC test 48 h later. Rats submitted to a plus-maze discriminative avoidance task (PMDAT) also were treated with harmine (5, 10, 15 mg/kg, i.p.) before the training. In this task, a regular elevated plus maze is used, but one of the closed arms will be equipped with visual and sound aversive stimuli. Every time the animal enters the aversive arm during training, the stimuli is continuously presented until the animal lefts the arm. Although during training all animals learned to avoid the aversive arm, indicating memory acquisition, 24 h later all harmine-treated groups were not significantly avoiding the aversive arm when compared with the other nonaversive arms (102).

Rats trained in a CFC protocol that received a single dose of ayahuasca (60 mg/kg) 20 min before or 3 h after a re-exposure session to the conditioned context present less freezing behavior when tested in the same context one day later. This decrease is not observed during the re-exposure session itself nor during the test when the animals are treated without being re-exposed to conditioned context previously to testing. Interestingly, the same results are reproduced even for remote memories, when the animals are tested 22 days after the re-exposure. These results suggest that ayahuasca could be acting on memory reconsolidation, reshaping the fear response as a consequence of the memory trace becoming more labile (12).

Regarding extinction protocols, the results are conflicting. The treatment with a single dose of DMT (10 mg/kg, i.p.) 1 h prior extinction training on TFC, as well as chronic treatment with smaller DMT doses (1 mg/kg, i.p.), seem to facilitate fear extinction (96, 100). However, in the CFC protocol, even multiple treatment-paired extinction sessions were not able to extinguish the fear response (96). On mouse submitted to TFC, psilocybin administration (2.5 mg/kg, i.p.) prior to extinction training decreased fear expression during training and during extinction tests 1 and 6 days after training (103).

AYA (adjusted to contain 0.3 mg/kg of DMT) administration to rats 1 h before a CFC extinction session decreases freezing behavior during the sessions, but the reduction is not sustained one day later on the extinction test. However, when the animal is submitted to two treatment-paired extinction sessions, the extinction memory is recalled when tested one day later (13). When the AYA (60 mg/kg) treatment was administered 20 min before or 3 h after a retrieval session, one day prior to extinction training, a single dose was sufficient to facilitate the acquisition of extinction memory (12). Chronic AYA treatment (120 mg/kg, oral) before CFC altered freezing expression, but did not affect extinction learning (99).

Even after extinction, re-exposing animals to the US can promote the reinstatement of the fear response. Treatment with AYA (60 mg/kg) 20 min before or 3 h after a retrieval session can prevent reinstatement after the acquisition of the extinction memory (12). However, when the treatment (adjusted to contain 0.3 mg/kg of DMT) is carried out during the extinction session, although the extinction memory is acquired, the reinstatement is not prevented (13).

The differences between the results observed for treatment with isolated compounds of AYA suggest the β-carbolines could be more effective targeting HPP-dependent memories, as is the case of CFC, step-down passive avoidance and PMDAT tasks. These amnesic effects can be an indication that β-carbolines are promoting increased neurogenesis, once increasing HPP neurogenesis on HPP-dependent tasks can promote forgetting (104). However, all available data test these substances on memory acquisition and early consolidation, while data regarding its effects on already established memory traces are still lacking (101, 102).

DMT, on the other hand, does not affect memory acquisition and early consolidation, although its administration before TFC enhances freezing response during the training. However, during extinction protocols for TFC, treating the animal with a single dose 1 h before the extinction session or a chronic treatment with smaller DMT doses can facilitate fear extinction, but the same result does not occur on CFC trained animals (96, 100). These results suggest that, although DMT can interfere with fear processing, it is not effective for targeting HPP-dependent memories.

When AYA itself is being tested, the extinction and reconsolidation efficacy was linked to duration and frequency of exposure to the conditioned context. Extinction retention was dependent on animals being re-exposed to the conditioned context at least two times (12, 13). The current most widely accepted view on consolidation of recent into long-term memories posits that during this process the memory trace will increasingly rely more on cortical than on HPP activation (105). However, prolonged re-exposure to the conditioning context can lead to HPP activation, which then can make the already established memory once again susceptible to neurogenesis induced forgetting (104, 106). These data are reminiscent of exposure therapy protocols currently being employed to treat PTSD (31, 107). The effect of AYA on TFC reconsolidation and/or extinction protocols still needs to be tested.

Although these studies suggest that AYA and its components modulate fear memory processing, the conditioning protocols tested responses induced by nonpathological fear memories, since no protocol induced generalized fear behavior and most treatments did not increase anxiety-like responses when tested using the EPM (12, 13). The question remains whether the outcomes would be different when tested for pathological-like memories.

Trauma focused therapeutic interventions are currently widely employed and advised for treatment of PTSD (108). These interventions are based on the previously discussed premise that memory recall can facilitate the alteration of emotional and behavioral responses associated to the memory trace. However, even though data supporting trauma-focused therapies are the most robust for all currently employed therapeutic strategies, they are not always effective and, in many cases, the improvement is not sufficient to abolish PTSD diagnosis (109). Additionally, there is also reported variability in pharmacological treatment efficacy when comparing different traumatic events. For example, cannabidiol (300 mg) is effective in reducing anxiety and cognitive impairment triggered by traumatic memory recall only for nonsexual trauma (110).

Among other things, this variability can be a consequence of different symptomatology. The fifth edition of the Diagnostic and Statistical Manual for Mental Disorders (DSM-5) recognized a dissociative PTSD subtype, characterized by the presence of depersonalization and derealization symptoms (111). Compared with nondissociative PTSD, this subtype seems to be linked to increased cortical inhibition of limbic structures (112). In patients with borderline personality disorder, higher prevalence of dissociative experiences was a predictor for impaired acquisition and extinction of an AMY-dependent classic conditioning task (113).

Although animal models can be useful to understand different interventions outcomes on specific circuits, they lack precision to evaluate specific symptoms. Broadening the understanding of how PTSD can alter patients' brain functioning is essential to the development of better models.

Evidence for Ayahuasca' Effects on Fear and Anxiety Responses in Humans

Neuroimaging techniques used to investigate how AYA intake alters neural substrates suggest that it modulates structures and networks relevant to emotional processing.

In one study, healthy male subjects were randomized to receive AYA (adjusted to contain 1 mg/kg of DMT) or placebo and 100–110 min after intake participants were submitted to single photon emission tomography (SPECT) to assess how AYA altered regional cerebral blood flow (rCBF). Compared with placebo, AYA bilaterally increased rCBF on anterior insula and inferior frontal gyrus, increased rCBF on the right anterior cingulate and frontomedial cortex, and on the left AMY and parahippocampal gyrus (114). Another SPECT study, this time evaluating depressive patients, compared rCBF prior to and 8 h after AYA intake (2.2 mL/kg). The treatment increased rCBF on left nucleus accumbens, right insula and left subgenual anterior cingulate cortex (11).

Functional magnetic resonance imaging (fMRI) was used to assess AYA effects on the default mode network (DMN) in healthy volunteers.

Subjects were evaluated before and 40 min after AYA intake (2.2 mL/kg) when performing a verbal fluency task or during resting state. Results contrasted DMN signal during resting state and during task performing, and a decrease in signal was reported for the anterior and posterior cingulate cortices, mPFC, precuneus and inferior parietal lobules (115).

Hallucinogens effects evaluated through social cognition tasks can also be useful to better comprehend how these substances can alter emotional processing. Studies with healthy and clinical samples have been performed to evaluate how they can interfere with REFE.

A study with healthy volunteers compared how different LSD doses (100 or 200 μg) could alter REFE performance when compared with placebo. Subjects were tested 5 h after intake of the lower dose and 7 h after intake of the higher one, and both doses decreased accuracy for recognition of fearful expressions (116). Another study by the same group used fMRI to compare how healthy individuals respond when presented to fearful or neutral expressions. Each subject received 100 μg of LSD or placebo 2.5 h before the scan. Compared with placebo, LSD reduced neural response to fearful versus neutral faces on left AMY and right medial frontal gyrus. The AMY activation to fearful faces was also negatively correlated to reported subjective drug effects (117). Also, administration of psilocybin (215 μg/kg) to healthy subjects decreased the recognition of negative facial expressions when compared with placebo (90).

Regarding AYA, healthy volunteers were submitted to fMRI before and after drug intake (25–35 mL, 0.333 ± 0.056 mg/kg DMT), and asked to perform a task with implicit emotional stimuli (neutral, disgusted or fearful facial expressions). Before AYA intake, reaction time was longer when aversive stimuli were presented, but during the AYA effects, the reaction time was no longer different for neutral and aversive stimuli. Together with the behavioral alterations, AMY responsiveness to aversive stimuli was attenuated by AYA, while the anterior insula and the dorsolateral PFC responsiveness increased (118). Similarly, increases in reaction time in a REFE task were observed in healthy volunteers after a single AYA dose (1 mL/kg; ±0.72 mg/mL DMT) (119). On the other hand, a previous study evaluating the effects of a single dose of ayahuasca (1 mL/kg; ±1.58 mg/mL DMT) in healthy volunteers did not identify behavioral differences on REFE performance when compared with the placebo group (120). However, these studies did not assess parameters regarding neural activity, which could be altered even in the absence of behavioral outcomes.

Although the clinical evidence assessing the effects of AYA on fear and anxiety disorders is still scarce, a few observational and experimental studies with healthy subjects explored its effects on trauma, memory, anxiety and phobia measurements.

Long-term members of ayahuasca churches in Brazil (over 15 years), when compared with actively practicing religious individuals from catholic and protestant churches, showed lower scores on phobic anxiety availed through the Symptom Checklist 90 – Revised (SCL-30-R), a self-report inventory to assess psychopathologies (121). An observational, naturalistic study conducted with healthy participants taking part on a AYA traditional indigenous retreat in Peru used the Sentence Completion for Events from the Past Test (SCEPT) to evaluate how the hallucinogenic experience could alter their perception of autobiographical memories, and a significant reduction on scores for negative valence memories was observed when comparing the baseline with postretreatment at the 6 months follow-up. However, it is important to point out that these participants did not present a high level of traumatic childhood experiences, as assessed through the Childhood Trauma Questionnaire scores collected on baseline (14).

An experimental double-blinded study with experienced members of an AYA church assessed panic and anxiety outcomes during the substance peak effects (1 h after ingestion). AYA (3 mL) and placebo scores were compared with baseline, and only AYA was effective in reducing panic-related signs assessed through the Anxiety Sensitivity Index. Anxiety was assessed using the State-Trait Anxiety Inventory (STAI), but the placebo and AYA scores did not differ from baseline (122).

Another study investigated the subjective effects of AYA (1 mL/kg; ±0.72 mg/mL DMT) combined with placebo or cannabidiol (600 mg) on healthy subjects using the Visual Analogue Mood Scale (VAMS). During AYA effects participants reported a decrease in anxiety, independently from the pretreatment group (119).

Regarding clinical populations, a recent case series reported the use of AYA to treat PTSD in war veterans taking part in a retreat. The Post-traumatic Stress Checklist (PCL-5) was used to assess PTSD symptoms and to evaluate clinical changes through the protocol. Most participants (7 out of 8) lowered PCL-5 scores after the intervention, and 5 of them still had lower scores 3 months after the intervention when compared with baseline. More than half of the participants reported intensely experiencing intrusive memories of the traumatic event. After the intervention, the largest improvements were observed in Cluster E symptoms, concerning sleep disturbances, hypervigilance, and concentration difficulties, and although some participants reported a reduction on intrusive memories, it was not statistically significant (15).

AYA was also tested in a randomized, placebo-controlled trial with subjects diagnosed with social anxiety disorder. Participants received a single dose of ayahuasca (2 mL/kg, ±0.68 mg/mL DMT) or placebo and, after the acute effects (300 min after intake), they were submitted to the SPST. During the protocol, anxiety and self-perception of performance were assessed using the VAMS, the Beck Anxiety Inventory and the State Version of the Self-statements During Public Speaking Scale. No significant differences were found between groups on the anxiety measures, but the AYA group showed improved perception of performance when compared with placebo (7).

The observational and experimental data available imply that ayahuasca might be a potential treatment for anxiety and stress disorders; however, there is a lack of studies with clinical populations conducted on controlled settings. Since AYA is an element of traditional cultures, there is an inherent challenge on variability control of AYA studies. It cannot be manufactured with commercial purposes, and the absence of standardized procedures lead to brew batches with highly diverse alkaloid composition and concentration, which reflects on the dosage variability present in naturalistic and experimental settings.

Synthetic formulations are already being tested as a possible alternative to try improving this variability, and to try to deal with ethical problems attached to the use of traditional formulations (123).

Ayahuasca Effects on Fear and Anxiety Responses Through 5HT Signaling

The currently available data suggest that AYA and its constituent substances, that is, DMT and β-carbolines, can modulate fear and anxiety responses. However, molecular and functional data supporting the behavioral and clinical observations are still scarce.

Neuronal and synaptic plasticity mechanisms are a fundamental aspect supporting behavioral flexibility. Increasing effort has been made into elucidating psychedelic induced plasticity, and it is possible that they hold the answer for the fast-acting therapeutic properties these substances apparently have.

Similarly to other psychedelic substances, DMT can promote increased neuritogenesis and synaptogenesis on cortical neurons. This effect is possibly mediated by BDNF interaction with TrkB receptors and subsequent activation of mTOR intracellular signaling pathways (18). Mice chronically treated with harmine (20 mg/kg, i.p. for 10 days) also present increased BDNF expression on the PFC (124) (Figure 1A). In humans, healthy and depressive participants receiving a single AYA dose (1 mL/kg) expressed increased BDNF serum levels 48 h after intake when compared with placebo groups (125).

On cortical neurons, DMT plasticity increasing properties are dependent on 5HT2A receptors activation (18). However, injection of a 5HT2A antagonist into the IL did not prevent AYA facilitation of extinction learning and recall on rats previously submitted to CFC, even though it increased freezing levels during extinction sessions (13). The increased freezing expression might be due to a decrease in the inhibitory control over central AMY projections, since the IL PNs innervate the ITC which then inhibits central AMY (126) and the PNs activation might be regulated by the 5HT2A receptor.

Increased plasticity at the IL is necessary for extinction memory retention (127); however, 5HT2A antagonism did not impair extinction

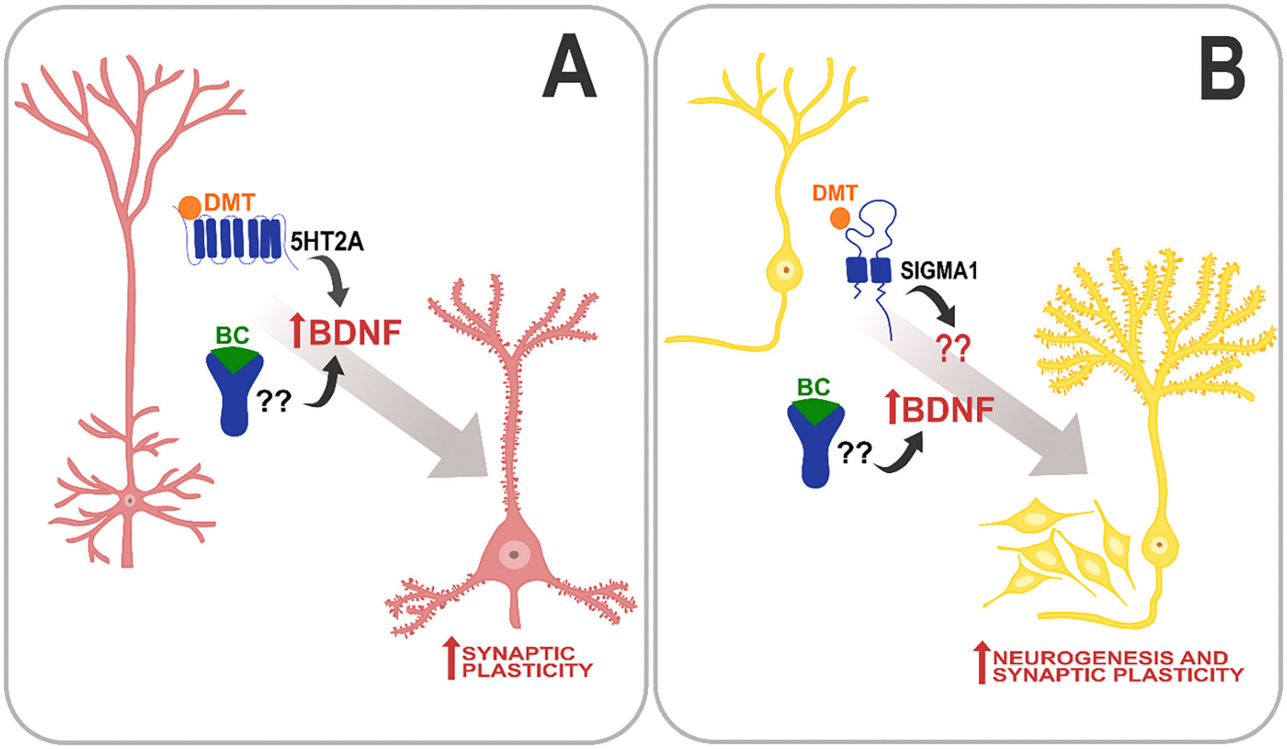

Figure 1. Plasticity-promoting mechanisms triggered by DMT and BC. (A) DMT and BC-induced increase in cortical plasticity are linked to enhanced BDNF levels, although this might result from activation of different receptors. (B) Increased hippocampal plasticity and neurogenesis induced by DMT and BC rely on different molecular pathways. 5HT2A: serotonergic receptor 2A subtype; BC: β-carboline; BDNF: brain-derived neurotrophic factor; DMT: N,N-dimethyltryptamine; SIGMA1: sigma receptor subtype 1.

learning. A possible explanation is the fact that extinction learning relies on BDNF increase on HPP inputs to the IL (128), so even though 5HT2A antagonism could prevent DMT induced plasticity at the IL, the extinction memory was not affected.

On the other hand, the same protocol testing a 5HT1A antagonist prevented AYA effects on extinction retention or recall, although it did not alter the decrease in fear expression during extinction learning (13). IL projections to BLA are necessary for extinction retention (129), and these data suggest that this effect might be mediated by 5HT1A activity. The IL projects to BLA PNs and INs, and during fear extinction synaptic efficacy of PNs innervation is reduced through a process that might resembles a long-term depression (126). Since 5HT1A receptors are relevant to modulate input-generated excitability on cortical PNs, it is possible that they are involved in the synaptic efficacy decrease. AYA and DMT acute treatments in rodents can lead to an increase in anxiety-like responses on EPM and FST, despite also inducing an antidepressant effect on the FST (95, 96). This increase in conflict anxiety responses could be a consequence of 5HT2A receptor activation by these compounds. Interestingly, different from what is observed after AYA and DMT administration, β-carbolines do not induce an increase in anxiety-like response despite their mild affinity for 5HT2A receptors (98)

Harmine chronic administration (20 mg/kg, i.p. for 10 days) can increase HPP neurogenesis in mice (124), which could also explain the behavioral outcomes of β-carbolines administration on HPP-dependent tasks (Figure 1B). Opposingly to the effects of 5HT2A activation on cortical neurons, on the HPP this receptor is not linked to plasticity increase. Rats treated with DOI, another psychedelic compound, present decreased HPP BDNF mRNA expression, whilst still having increased BDNF levels on cortical areas. This modulation was completely blocked by a 5HT2A antagonist administration. Interestingly, immobilization stress also results in a decrease in BDNF mRNAs on the HPP through 5HT2A activation (130).

Hence, 5HT2A activation on the HPP possibly does not contribute to the antidepressive and might be responsible for the anxiogenic DMT effects. Nevertheless, DMT treatment can induce neurogenesis on HPP, but the mechanism seems to result from sigma-1 receptors activation instead (131) (Figure 1B).

It is possible that the β-carbolines effect on depressive-like behaviors as well as in HPP-dependent memories could rely on its antagonism of monoamine oxidase enzymes, that could increase circulating levels of 5HT. Additionally, since they do not present affinity for 5HT1A receptors, they would not activate the raphe nuclei autoreceptors, preventing the decrease in 5HT release observed after acute administration of 5HT1A agonists (79, 132).

Possibly, β-carbolines administration could somehow predominantly activate specific raphe nuclei pathways, since the behavioral responses observed after its administration resemble the median raphe forebrain bundle tract mediated responses. This pathway directly controls HPP activity, and increased activity in this circuit is linked to antidepressant behavioral responses (133). Also, this pathway stimulation can desynchronize HPP theta oscillations, which are relevant for associative memory processing (134). This could explain why β-carbolines treatment seems to be more effective on interfering with HPP-dependent memory processing. The anxiety-like responses evoked by acute treatment with DMT suggests this substance might be acting on substrates innervated by the DRD/DRC projections and would explain the lack of effects of DMT treatment on CFC extinction, since this task is HPP-dependent. On the other hand, β-carbolines preferential effect on DRI/MnR pathway could explain the lack of treatment-induced anxiety-like behaviors, despite their mild 5HT2A affinity, besides the antidepressant properties and amnesic effects on HPP-dependent memories processing.

Future Perspectives

Although AYA has been employed in therapeutic and religious contexts for centuries, there is still a lot to be dissected on its biological and psychological effects. The complex nature of this brew, that combines different alkaloids, adds another layer of intricacy to an already challenging task.

In currently available literature, DMT is frequently mentioned as the main psychoactive constituent of AYA, however many studies discussed throughout this review highlight relevant differences on isolated DMT effects when compared with AYA or β-carbolines. Although β-carbolines lack the mind-altering properties of AYA and DMT, they seem to have therapeutic properties as well. More studies investigating the molecular pathways supporting antidepressant and memory effects elicited by them could improve comprehension on AYA, as well as indicate contexts where isolated β-carbolines could be employed as treatment. Hereof, differences on HPP plasticity and neurogenesis molecular pathways activated by DMT and β-carbolines could clarify the distinct behavioral outcomes promoted by these substances.

Regarding human studies, there is still a long way to go. The observational and experimental studies investigating healthy populations support the relevance of further investigations; however, clinical studies are still lacking, especially in controlled settings. The unknown risks that psychedelic intake can represent to specific clinical populations together with the prejudice accumulated from years of criminalization are some of the challenges faced by the researchers. On top of that, the increasing hype around psychedelic therapeutic effects can result in a positive bias. Controlling this bias is also a difficult task, since blinding is still a challenge for the field.

Final Remarks

In an attempt to associate the emerging data on hallucinogens therapeutic properties for treatment of mental disorders and the classical Deakin/Graeff theory linking fear and anxiety responses to 5HT signaling, Carhart-Harris and Nutt (2017) propose that hallucinogen-induced 5HT2A agonism, and the subsequent activation-induced plasticity, mediate active coping in a similar idea to the DRD/DRC projections. In the same review, they also propose that passive coping would be the mechanism supporting conventional antidepressants efficacy, such as SSRIs, and would be mediated by 5HT1A activity, similarly to the DRI/MnR pathway (135).

Through that perspective, AYA therapeutic properties could be a combination of active and passive coping mechanisms. The β-Carbolines apparent capacity to modulate HPP activity, in what they call passive coping, could be a relevant factor behind AYA effects on CFC extinction that could not be reproduced by DMT treatment. DMT, on the other hand, seem to behave similarly to what is proposed for other classic hallucinogens, favoring active coping strategies and mechanisms.

Author Contributions

LTLG, MSc prepared the original draft. RGDS, PhD intellectual conceptualization, review and editing the manuscript. JECH, MD, PhD intellectual conceptualization, review and editing the manuscript.

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Author Disclosures

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