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5. The therapeutic potential of harmine and ayahuasca in depression: Evidence from exploratory animal and human studies

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Abstract. The high prevalence and the socio-functional impairment associated with depressive disorders, added to the limitations of currently available treatments, justify the search for novel pharmacological strategies for the management of depression. This chapter presents the major results of animal and human studies conducted by a group of Brazilian researchers concerning the antidepressant potential of harmine, an alkaloid belonging to the group of β-carbolines and present in Ayahuasca (AYA), a tea with hallucinogenic properties used for religious and medicinal purposes

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by peoples from the Amazon. The results obtained thus far suggest that harmine and other substances present in AYA might have antidepressant-like effects in the central nervous system of animals and human patients, pointing out the possibility of the therapeutic use of AYA in humans.

1. Depressive disorders – Clinical aspects

Depression is a highly frequent psychiatric disorder with a lifetime prevalence of 17%, being twice as prevalent among women as compared with men. Onset usually occurs in the third decade of life, but the disorder can affect individuals at any age. It is a recurring condition and around 20-25% of patients become chronically ill[1]. Depressive disorders are associated with intense suffering, high morbidity rates, and increased mortality[2]. According to a study of the World Health Organization (WHO), depression is currently the fourth leading cause of morbidity and, within a ten-year period, it might rank second among the disorders affecting productive life[1].

According to the current Diagnostic and Statistical Manual of Mental Disorders published by the American Psychiatric Association (DSM-IV)[3], the diagnosis of a depressive episode requires the presence of depressed mood and/or anhedonia for a minimum of two weeks, accompanied by at least four of the following symptoms: significant weight loss or gain (5% of body weight); psychomotor agitation or retardation; insomnia or hypersomnia; fatigue or diminished energy; low self-esteem or inappropriate feelings of guilt; difficulties to think, concentrate or make decisions; and thoughts of death and suicide ideation or attempt. The symptoms must be associated with significant suffering and/or impairment in social, occupational or other functional areas, cannot be caused by a general medical condition or substance use, or fulfill the criteria for a mixed episode (episode in which the diagnostic criteria for both depression and mania are simultaneously satisfied).

Clinically, depressive disorders are divided into single episode (if only one episode has occurred in life), recurring (when at least two episodes occurred), and chronic (if an episode lasts for two years or more)[3]. In terms of severity, depressive episodes are divided into mild, moderate, and severe. In mild episodes, few or no additional criteria besides those necessary for diagnosis are fulfilled and functional impairment is minor; in severe episodes a variety of symptoms are present, with significant functional impairment and possible association with psychotic symptoms; in moderate episodes, both the number of symptoms and the ensuing functional impairment lie on an intermediate level between the two former categories[3].

2. Etiologic factors and neurobiology of depression

The vulnerability to develop depression is connected with environmental factors such as early parental loss, childhood history of traumatic events, personality traits, family and personal history of depression, recent traumatic events, and genetic factors[1].

One of the main hypotheses to explain the neurobiology of depression was proposed following the discovery of the mechanisms of action of early antidepressant agents, which were accidentally discovered in the 1950s during the development of antihistamine (imipramine → tricyclic antidepressant) and antituberculosis (iproniazid → monoamine oxidase (MAO) inhibitor) drugs. Added to this, the comprehension of the action of three substances on the central nervous system (CNS), namely, imipramine (inhibiting neuronal reuptake of noradrenaline and serotonin), reserpine (depleting monoamines and causing depressive symptoms), and amphetamine (releasing noradrenalin and inhibiting its neuronal reuptake, causing euphoria) led to the proposition, in the 1960s, of the classic monoamine theory of depression, according to which the disorder would be caused by decreased availability of noradrenaline and serotonin in the brain[4].

These discoveries were followed by the development of new antidepressants, with similar mechanisms of action but better side-effect profiles and easier management, which are widely used in today's practice, such as serotonin and noradrenaline selective reuptake inhibitors[5].

The serotonergic and noradrenergic systems, which are involved in the pharmacology of antidepressants, project from nuclei located in the brain stem onto wide areas in the midbrain. Noradrenergic neurons project from the locus coeruleus, whereas serotonergic neurons project from the raphe nuclei[4]. Fourteen serotonin receptors, divided into seven classes, have been identified to date. Together with other neurotransmitters, serotonin mediates such diverse aspects as mood, anxiety, sleep, body temperature, eating and sexual behavior, gastrointestinal motility, and others[6].

Many antidepressant drugs act primarily by increasing extracellular concentrations of serotonin, which leads to alterations in many receptors, resulting in therapeutic effects secondary to late neurochemical alterations. The activation of pre-synaptic 5-HT1A receptors in the raphe nuclei normally leads to decreased serotonin release. Antidepressant drugs that act by inhibiting the reuptake of serotonin cause the desensitization of these receptors, thus stimulating the release of serotonin by neurons and increasing the serotonergic neurotransmission. This hypothesis would explain the time

required for antidepressant drugs to present their therapeutic effects, since these are dependent on neurochemical adaptations[6].

3. Treatment of depression

A number of alternatives are available today to treat depression, encompassing antidepressant drugs, psychotherapy, electroconvulsive therapy, and other somatic treatments.

In respect to the pharmacological management of the disorder, it is clear that the discovery of antidepressants in the 1950s brought about a revolution in the treatment of depression, standing out among the other therapies available[2]. Currently, different classes of antidepressant agents are available, which are classified according to their effects on the neuronal synapse, their action on MAO or on their chemical structure.

Tricyclic antidepressants (TCA) and MAO inhibitors (MAOI) are known as "first generation" or "classic" antidepressants. Both these groups act by increasing the extracellular availability of monoamines – TCAs via inhibition of serotonin and noradrenaline reuptake, and MAOIs via inhibition of the metabolism of these neurotransmitters[7]. Besides the action described above, which is responsible for their therapeutic effects, TCAs act upon many other receptors, presenting antimuscarinic, antihistaminic, and anti-α2 adrenergic effects that may cause undesirable reactions such as urinary retention, constipation, orthostatic hypotension, weight gain, and somnolence. Additionally, TCAs block the sodium channels, interfering on nervous transmission and being potentially arrhythmogenic[4,7]. Concerning MAOIs, their main adverse effect is the risk of hypertension crises triggered by the intake of food containing tyramine, a sympathomimetic amine occurring in large quantities in certain foods and which is metabolized by MAO[4].

Newer antidepressants have been designed to be more selective. Among these are the selective serotonin reuptake inhibitors (SSRIs: fluoxetine, paroxetine), selective noradrenaline reuptake inhibitors (reboxetine), serotonin-noradrenaline reuptake inhibitors (venlafaxine, minalcipran, duloxetine), and other antidepressants with multiple mechanisms of action, such as mirtazapine, which acts as a pre-synaptic α2-noradrenergic antagonist and as an antagonist of serotonin receptors (5-HT2 e 5-HT3), and nefazodone, which acts both by inhibiting the reuptake of serotonin and noradrenaline and by antagonizing α2 and 5-HT receptors[7]. Although the side-effects of these drugs are not as significant as those of earlier antidepressants, they are still present in more recently developed psychopharmacological agents[3].

The efficacy of newer antidepressants is not different from the efficacy of compounds developed earlier, and although around 80% of the patients respond to the treatment with antidepressants, only 50% present full remission[5].

In summary, the limitations associated with the currently available pharmacological treatments of depression are: low response rates, side-effects, and time required until therapeutic effects are attained. Thus, novel pharmacological strategies, especially those with acute effects, would have an important impact on the treatment of depression[8].

4. Ayahuasca

Ayahuasca (AYA) is a beverage with hallucinogenic properties used for religious and medicinal purposes by peoples of South America, markedly in the Amazon, and there is evidence of its use since antiquity[9]. Ayahuasca is made from sections of the *Banisteriopsis spp.* vine usually boiled with other plants. The species of these plants most commonly used in the preparation are *Banisteriopsis caapi* and *Psychotria viridis*[10]. *Banisteriopsis caapi* contains the alkaloids harmine, tetrahydroharmine (THH) and, in a lower quantity, harmaline, all of which belong to the group of β-carbolines; whereas *Psychotria viridis* supplies the hallucinogenic substances tryptamine *N*,*N*-dimethyltryptamine (DMT) [10-12].

The hallucinogenic effect of AYA derives from the potent serotonergic action of DMT in the CNS, particularly on 5-HT2A and 5-HT2C receptors[10,13-15]. The psychoactive effects of AYA are thus mediated by the action of β-carbolines, specifically harmine and harmaline, which act upon MAO [9,10,12]. Tetrahydroharmine (THH), the second most concentrated β-carboline in AYA, acts as a weak serotonin reuptake and MAO inhibitor[10].

Peripheral inhibition of MAO allows the proper levels of DMT in the beverage to reach the CNS, causing intense – however short-lasting – perceptual, cognitive, and affect alterations. The main of such alterations are a predominant sensation of well-being; a fleeting feeling of apprehension; complex thoughts; novel experiences about one's identity; vivid images (visible even when the eyes are closed); visual alterations of color, shape, and movement of objects; a sensation of having a clearer perception of sound; and an altered sense of touch. These subjective effects start 35-40 minutes after the ingestion of the tea, reaching maximal intensity between 90 and 120 minutes and ending after 4 hours[11,12,16]. Differently from what happens with other hallucinogenic substances, the repeated administration of DMT is

not associated with the development of tolerance to its psychotomimetic effects, and there is no desensitization of 5-HT2A receptors[13,17].

Scientific investigations on AYA from the perspective of its interest to pharmacology and mental health began in the 1970s. Investigations involving members of the *União do Vegetal* (Vegetal Union) religious group underscored the high prevalence of psychiatric disorders prior to the beginning of the ritual use of the beverage, comprising particularly alcohol and substance abuse and dependence, but also depression and social phobia. Nevertheless, there are no reports of members presenting with current psychiatric disorders at the time of evaluation, with reports of remission following the beginning of the use of the tea. It is important to highlight that there were no reports of recurrent substance use since the beginning of tea intake (for periods over 10 years) and that there are no reports of AYA abstinence[10,11].

One study investigated the acute effects of the ingestion of AYA in members of the *Santo Daime* (Holy *Daime*) religion using measures of anxiety, panic, and hopelessness. The authors found that those participants who were under the effects of AYA had lower ratings of these symptoms compared with participants receiving placebo[18].

Together, these reports encourage the investigation of the possible therapeutic applications of AYA in humans.

5. Ayahuasca and depression

5.1. Antidepressant-like effects of β-carbolines and serotonergic agonists

Harmine, the β-carboline with the highest concentration in AYA, interacts with distinct systems: in the CNS, harmine actions have been reported on MAO-A, 5-HT_{2A} and imidazoline receptors (I_1 and I_2 sites), and cyclin-dependent kinases (CDK1, 2, and 5), but its wide pharmacological spectrum also includes antiplasmodial, antimutagenic, and antigenotoxic activity, and antioxidative, antidiabetic, and antiplatelet properties[19].

Animal studies conducted by Brazilian researchers investigated the antidepressant-like effects of harmine. Fortunato and colleagues[20] used the depression-inducing forced swimming test in rodents to compare the behavioral and molecular effects of acute harmine administration with imipramine and placebo. The forced swimming test is performed using a cylindrical water tank in which the animal is placed and behavioral parameters are measured (immobility, climbing, and swimming time). Figure 1 shows that acute treatments with harmine and imipramine were associated with decreased immobility time and increased swimming and climbing.

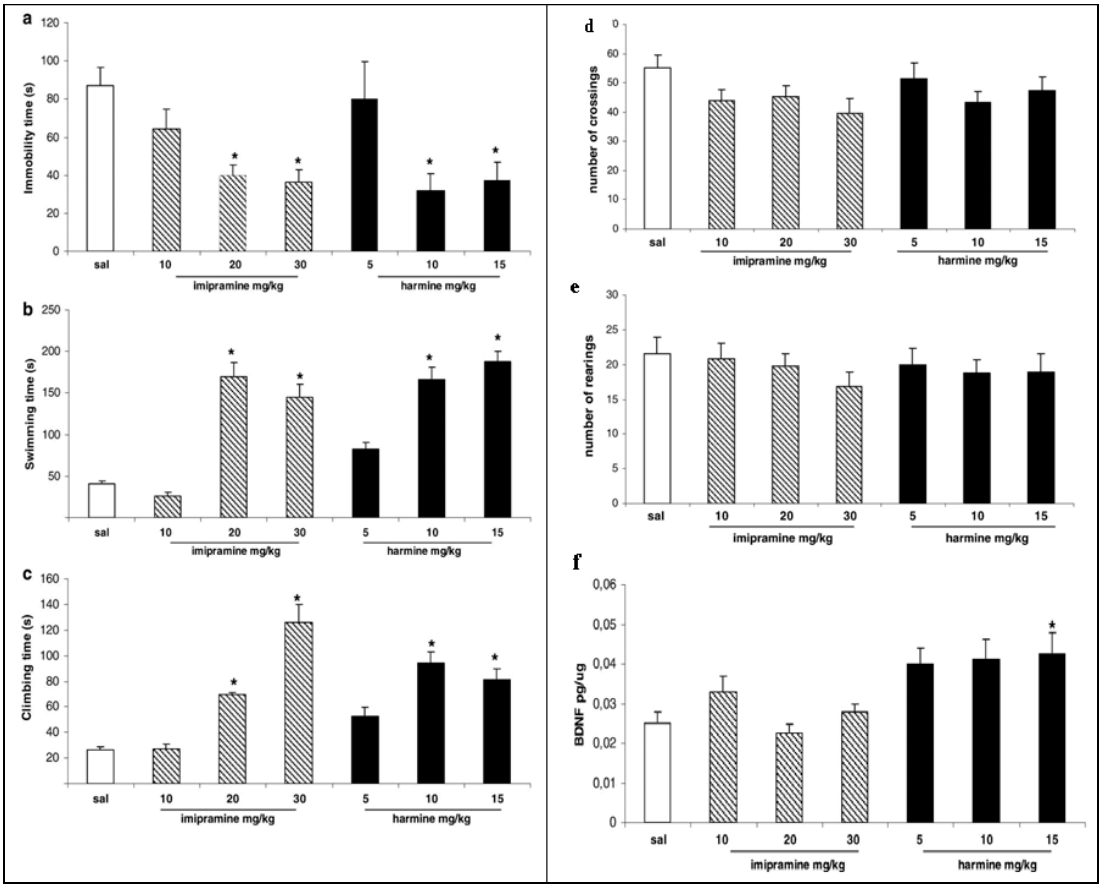


Figure 1. Effects of acute administration of harmine and imipramine on immobility time (a); swimming time (b), climbing time (c), number of crossings (d), number of rearings (e) and BDFN levels (f) in the hippocampus of rats subjected to the open-field test (adapted from Fortunato et al, 2009).

The acute treatment with harmine, but not imipramine, was also associated with increased levels of brain derived neurotrophic factor (BDNF) - which has an antidepressant action in the brain - in the rat hippocampus. Since these findings could reflect a general increase in spontaneous locomotor activity, the rats were submitted to the open-field test, and harmine and imipramine were not found to provoke increased spontaneous locomotion, which indicates a specific action of both compounds on the behavioral parameters related to depression in the forced swimming test.

Another study, also conducted by Fortunato and colleagues[19], was aimed at assessing the antidepressant properties of harmine using an animal model known as chronic mild stress (CMS). This model is believed to induce anhedonia (loss of interest or pleasure), a major feature of depression, reflected by the decreased intake of sucrose by rats. During a 40-day period, the animals were submitted to the following stressors: food and water deprivation, forced

swimming, flashing light, isolation, physical restraint, and cold. Figure 2 shows that the test was successful in inducing anhedonia, in addition to increasing adrenal gland weight and ACTH and BDNF levels. The administration of harmine was associated with reversal of all these effects.

The findings of these studies lend support to the view that harmine is an important candidate for the pharmacological management of depression and encourage new studies involving the use of this compound in humans.

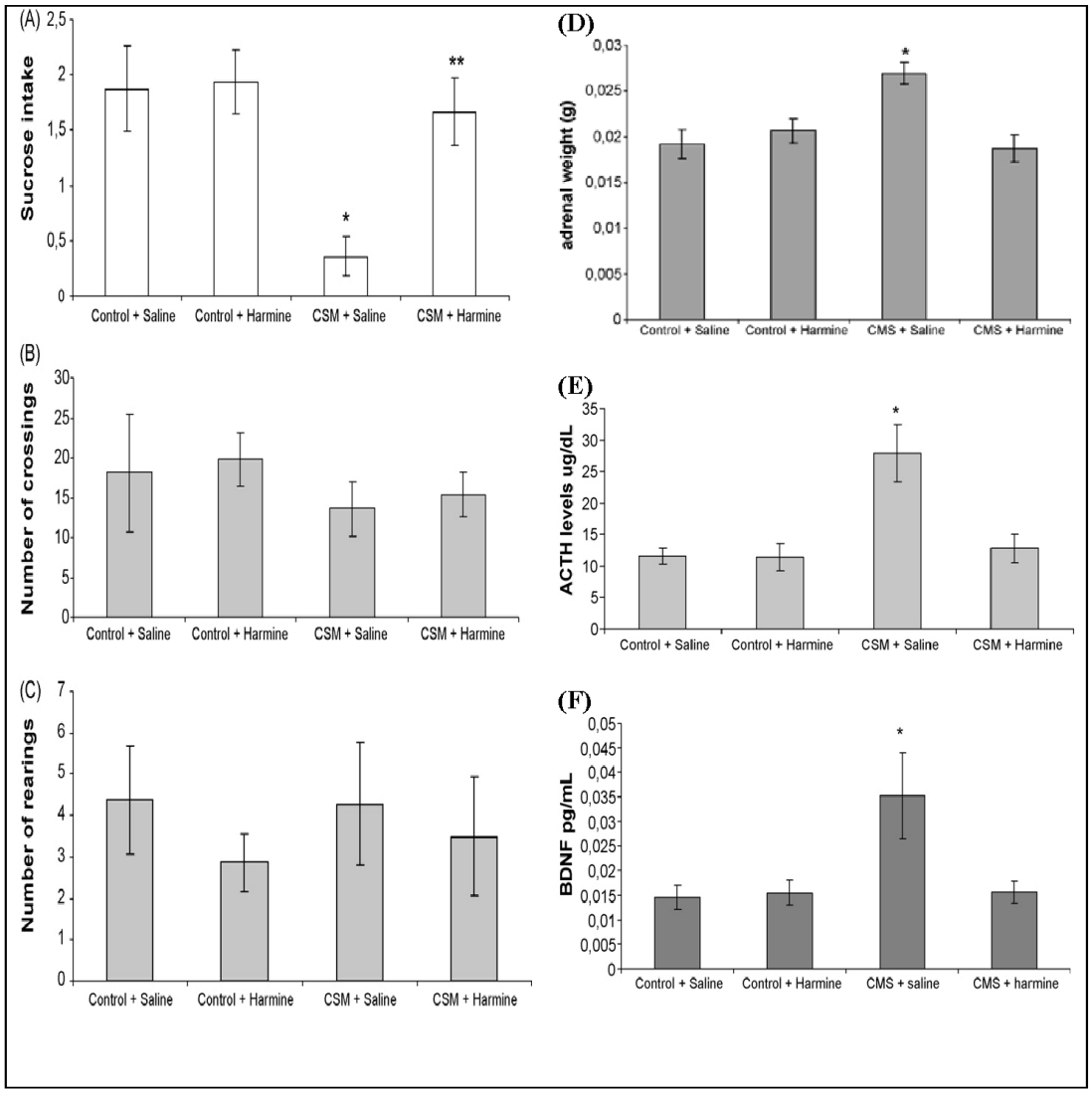


Figure 2. Effects of the CMS procedure on sweet food consumption (A), number of crossings (B), rearings (C), adrenal gland weight (D), adrenocorticotropic hormone (ACTH) (E), and BDNF levels in hippocampus (F) in rats chronically treated with harmine or saline(adapted from Fortunato et al, 2010).

5.2. Therapeutic trials with AYA in humans

Taking into account the positive findings concerning the antidepressant-like effects of harmine in animal studies and the components and mechanisms of action of AYA in the CNS, studies with humans are currently underway to investigate their therapeutic potential in people with depression.

An exploratory study was conducted involving three female participants with a clinical diagnosis of recurring depressive disorder and current mild/severe depressive episode without psychotic symptoms. The subjects had not been in treatment with antidepressants for two weeks and received an oral dose of 2ml/Kg of AYA. The participants' mental state was assessed by means of psychiatric scales, including the Hamilton Depression Scale (HAM-D), 10 minutes prior to AYA administration and 40, 80, 140, and 180 minutes after intake, as well as on days 1, 2, 7, 14, and 28 after drinking the tea.

The distribution of the subjects' scores in the HAM-D is shown in Figure 3. A significant decrease in the scores over time can be seen, starting at 40 minutes after intake, pointing out a reduction in depressive symptoms regardless of episode severity. A sustained reduction in the scores of depressive symptoms is observed from day 1 (of around 79% in relation to baseline) to day 14 (around 66% below baseline), when an expressive increase in depressive symptoms is seen towards baseline levels.

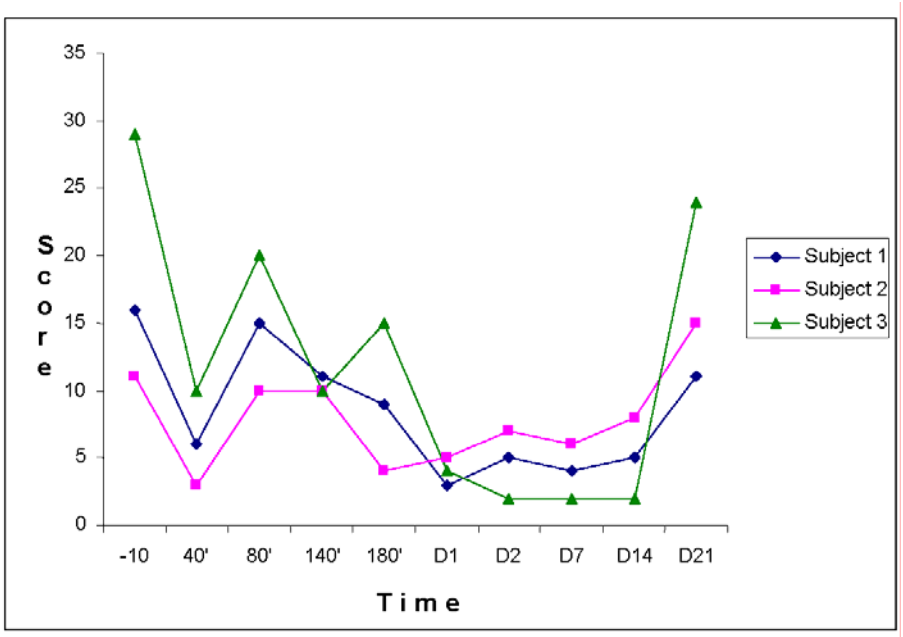


Figure 3. Effects of AYA intake on the final score of the HAM-D.

The items suffering the greatest variations over the duration of the experiment were those related to depressed mood, guilt feelings, suicidal ideation, difficulties at work activities, psychic anxiety, and genital symptoms.

It is important to mention that, although adverse effects associated with AYA were not systematically evaluated, they were not spontaneously reported by the participants during the evaluation period. Effects associated with psychotic experiences, related to thought and sensory-perceptual alterations, were punctual and short-lived, signalizing the safety and good tolerability of AYA mentioned by some authors[9-12,16].

The data of the latter study suggest that AYA has antidepressant properties - mediated by its action on serotonergic pathways - that seem to have an acute profile. However, this evidence must be considered with caution because of the intrinsic limitations of exploratory studies involving small samples. Future investigations involving larger samples and control groups are warranted in order to further our current knowledge on the therapeutic potential of AYA and its side-effect and action profiles over a larger time span.

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