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Inhibition of alpha oscillations through serotonin-2A receptor activation underlies the visual effects of ayahuasca in humans

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Abstract
Ayahuasca is an Amazonian psychotropic plant tea typically obtained from two plants, *Banisteriopsis caapi* and *Psychotria viridis*. It contains the psychedelic 5-HT$_{2A}$ and sigma-1

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agonist *N*,*N*-dimethyltryptamine (DMT) plus β-carboline alkaloids with monoamine-oxidase (MAO)-inhibiting properties. Although the psychoactive effects of ayahuasca have commonly been attributed solely to agonism at the 5-HT_{2A} receptor, the molecular target of classical psychedelics, this has not been tested experimentally. Here we wished to study the contribution of the 5-HT_{2A} receptor to the neurophysiological and psychological effects of ayahuasca in humans. We measured drug-induced changes in spontaneous brain oscillations and subjective effects in a double-blind randomized placebo-controlled study involving the oral administration of ayahuasca (0.75 mg DMT/kg body weight) and the 5-HT_{2A} antagonist ketanserin (40 mg). Twelve healthy, experienced psychedelic users (5 females) participated in four experimental sessions in which they received the following drug combinations: placebo +placebo, placebo+ayahuasca, ketanserin+placebo and ketanserin+ayahuasca. Ayahuasca induced EEG power decreases in the delta, theta and alpha frequency bands. Current density in alpha-band oscillations in parietal and occipital cortex was inversely correlated with the intensity of visual imagery induced by ayahuasca. Pretreatment with ketanserin inhibited neurophysiological modifications, reduced the correlation between alpha and visual effects, and attenuated the intensity of the subjective experience. These findings suggest that despite the chemical complexity of ayahuasca, 5-HT_{2A} activation plays a key role in the neurophysiological and visual effects of ayahuasca in humans.

1. Introduction

Ayahuasca is a psychoactive plant tea used traditionally by the indigenous peoples of the Upper Amazon (Schultes, 1980) and in more recent times by healers and members of religious syncretic groups (Tupper, 2008). This tea is receiving increased attention from the general public and biomedical researchers (Frood, 2015). It has been used to help treat addiction (Fernández et al., 2014), and recent open-label studies have shown preliminary evidence of rapid and lasting antidepressant effects after a single dose (Osório et al., 2015; Sanches et al., 2016).

Although there are many variations in the preparation of the tea, the common ingredient is the malpighiaceous vine *Banisteriopsis caapi*. This plant is rich in β-carboline alkaloids, mainly harmine, harmaline and tetrahydroharmine (THH) (Riba, 2003). These alkaloids show monoamine-oxidase inhibiting properties (Buckholtz and Boggan, 1977a, 1977b), while THH is also a serotonin reuptake inhibitor (Buckholtz and Boggan, 1977a, 1977b). In addition to *B. caapi*, other admixture plants are frequently used in the preparation of ayahuasca. One of the most common in the context of modern use is *Psychotria viridis*. The leaves of this plant are rich in the psychedelic indole *N*,*N*-dimethyltryptamine or DMT (Riba, 2003).

DMT is structurally related to the neurotransmitter serotonin (5-hydroxytryptamine; 5-HT) and shows agonist activity at the 5-HT_{2A} and 5-HT_{1A} receptors. DMT also acts as an agonist at the trace amine associated receptor (TAAR) (Bunzow et al., 2001) and it is a substrate of the serotonin and the vesicle monoamine transporters (Cozzi et al., 2009). It has been suggested that using these uptake mechanisms, intracellular concentrations could reach higher values than in plasma and interact with the intracellular sigma-1 receptor (Fontanilla et al., 2009). This receptor modulates the activity of many other proteins, conferring stability against cellular stress, and promoting brain plasticity (Chu and Ruoho, 2016; Tsai et al., 2009).

When administered to humans parenterally, DMT induces intense modifications of the ordinary state of awareness with intense visual effects, but it is devoid of psychoactivity when taken orally (Riba et al., 2015) due to degradation by MAO (Suzuki et al., 1981), and cytochrome-dependent mechanisms (Riba et al., 2015). The presence of the MAO-inhibiting β-carbolines in ayahuasca prevents is enzymatic degradation and allows its oral bioavailability (Riba et al., 2003a).

In previous studies by our group, we found ayahuasca to induce a pattern of psychedelic effects with a slower onset and longer duration than those induced by DMT (Dos Santos et al., 2011; Riba et al., 2003a, 2001b). Neurophysiologically, ayahuasca induces broad-band power decreases in spontaneous electrical brain oscillations (Riba et al., 2002a) and associated reductions in intracerebral current source density (CSD) in certain brain areas (Riba et al., 2004). These reductions are particularly strong for oscillations in the alpha band of the EEG, with CSD reductions over the posterior visual cortex, an effect thought to reflect increased cortical excitability (Romei et al., 2008b). Analogous findings in the range of the alpha band have also been observed using magnetoencephalography and the psychedelic and serotonin-$_{2A}$ receptor agonist psilocybin (Muthukumaraswamy et al., 2013).

The aim of this study was to assess the contribution of serotonin-$_{2A}$ receptor to the neurophysiological and psychological effects of ayahuasca. We postulated that despite the combination of various pharmacological mechanisms in ayahuasca, the general psychedelic effects and decreases in current density depend on activation of the 5-HT_{2A} receptor. To test this hypothesis, we studied the interaction of a medium dose of ayahuasca (Riba et al., 2001b) and ketanserin, a 5-HT_{2A} receptor antagonist, in a group of experienced psychedelic users in a laboratory setting.

2. Experimental procedures

2.1. Participants

For ethical reasons, we only recruited individuals with prior experience with psychedelics. We wanted to avoid introducing