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The Therapeutic Use of Ayahuasca

Springer
Chapter 7
Hypotheses Regarding Ayahuasca’s Potential Mechanisms of Action in the Treatment of Addiction

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Abstract Drug addiction is an epidemic problem affecting millions worldwide with high rates of morbidity and mortality. Although the number of pharmacological options available to treat addiction has increased, these treatments demonstrate only modest efficacy. New treatments with improved efficacy rates and favorable side effect profiles are needed. Ayahuasca is a medicine that is increasingly being utilized to treat addictions. However, despite its growing popularity, the mechanisms underlying ayahuasca’s effectiveness as a treatment for addictions remain unknown. We propose biochemical, physiological, psychological, and transcendent hypotheses to explain how ayahuasca treats addictions.

Keywords Ayahuasca • Mesolimbic pathway • Harmine • Addiction • Dopamine • Serotonin • Dual deficit hypothesis • Neuroplasticity • Psycholytic therapy • Psychedelic therapy

Addiction: A Global Problem

Substance abuse and drug addiction are enormous global problems, with health and social costs exceeding $500 billion annually (United Nations Office of Drugs and Crime 2012). Each year more than 200,000 people die from abusing cocaine, heroin, and other drugs. In the United States, more than 22.6 million individuals...
had a substance abuse or dependence problem in 2010 (Substance Abuse and Mental Health Services Administration 2012). Nearly 15,000 people died from overdoses of prescription pain medications in 2008, and almost half a million emergency room visits resulted from misuse of prescription narcotics in 2009. In 2010, approximately 12 million people reported nonmedical use of prescription narcotics in the previous year (Center for Disease Control 2011).

Existing pharmacological treatments demonstrate only modest efficacy (Anton et al. 2006; Hughes and Cook 2006; Marsch 2002) and are associated with non-compliance (Fuller et al. 1986) and misuse (Yokell et al. 2011). Given the high morbidity and mortality rates, as well as the lack of effective treatments, new therapeutic options for drug addiction are desperately needed.

One potential treatment is a medicine known as ayahuasca. Created from plants indigenous to the Amazon rain forest, ayahuasca is utilized by indigenous healers in South America for a variety of purposes (Schultes et al. 1998). Recently, ayahuasca has gained notoriety as a treatment for addictions (Fabregas et al. 2010; Halpern et al. 2008). Centers utilizing ayahuasca to treat addictions have arisen in Peru, Brazil, Argentina, Uruguay, and Chile. Despite this medicine’s increasing popularity, the mechanisms by which ayahuasca treats addictions remain unclear. We propose biochemical, physiological, psychological, and transcendent hypotheses to explain ayahuasca’s effectiveness as a treatment for addictions.

Biochemistry of Ayahuasca

Ayahuasca is a medicinal tea that is prepared by boiling two plants together for several hours until only a thick liquid remains. The plants most commonly utilized are *Banisteriopsis caapi* and *Psychotria viridis*. *Banisteriopsis caapi* is a vine of the Malpighiaceae family. The bark and vine of this plant contain the beta-carboline alkaloids harmine, harmaline, and tetrahydroharmine (see Figs. 7.1, 7.2, 7.3), which function as monoamine oxidase inhibitors (MAOIs) (Metzner 1999).

Monoamines are a family of chemically related molecules that serve as neurotransmitters in the human nervous system. Monoamines include catecholamines (e.g., dopamine, norepinephrine, and epinephrine) and tryptamines (e.g., serotonin, melatonin, and DMT). When ingested orally, monoamines are degraded by enzymes in the gastrointestinal tract known as monoamine oxidases (MAOs). MAOIs are chemicals that block these enzymes (McKenna et al. 1984). In addition to their function as MAOIs, beta-carboline alkaloids also stimulate the release of...
dopamine from presynaptic neurons in the mesolimbic pathway of the brain (Brierley and Davidson 2012). This dopamine releasing effect may play a key role in the anti-addictive properties of ayahuasca.

*Psychotria viridis* is a shrub from the coffee family that contains N,N-dimethyltryptamine, or DMT. DMT is a naturally occurring tryptamine alkaloid that has been isolated from numerous animal and plant sources, including human cerebrospinal fluid. When smoked or snorted, DMT causes a rapid alteration in consciousness (Strassman 2001). DMT is structurally similar to serotonin (5-HT) (see Figs. 7.4, 7.5) and demonstrates an affinity for most serotonergic receptors (Keiser et al. 2009). DMT acts as an agonist at 5-HT1a, 5-HT2a, and 5-HT2c receptors (Dart 2004; Deliganis et al. 1991; Smith et al. 1998; Stahl 2008; Strassman et al. 1994). When ingested orally, DMT is broken down by MAOs in the gastrointestinal tract (McKenna et al. 1984; Shulgin and Shulgin 1997). However, when ingested simultaneously with the beta-carbolines present in *Banisteriopsis caapi*, the DMT from *Psychotria viridis* remains orally active (Mabit 2007). The beta-carbolines, acting as MAOIs, block the enzymatic degradation of DMT, allowing it to remain intact through the gut, into the blood, and then into the brain.
Biochemical Theory of Addiction

Addiction is a complex phenomenon that results from multiple, interrelated factors. On a biochemical level, dopamine (DA) in the mesolimbic pathway of the brain is critical to the development and reinforcement of addictions (Hyman et al. 2006). The mesolimbic dopamine pathway (MDP), also known as the “reward pathway,” is involved in motivation, pleasure, and reward (Stahl 2008). This pathway contains DA neurons whose cell bodies are found in the ventral tegmental area (VTA) in the midbrain. These neurons send axonal projections to areas of the limbic system including the amygdala, hippocampus, and medial prefrontal cortex, both directly and indirectly via the nucleus accumbens (Moore and Bloom 1978; Pierce and Kumaresan 2006; Ungerstedt 1971).

Pleasurable stimuli such as food, sex, and video games lead to DA release in the MDP. Dopamine then binds to DA receptors, which are a class of G-coupled protein receptors. Five types of DA receptors have been identified, known as D1, D2, D3, D4, and D5. Dopamine receptors are generally divided into two subtypes, “D1-like receptors” (D1 and D5) and “D2-like receptors” (D2, D3, and D4) (Camí and Farre 2003).

Genetic factors, such as variations in the D2 receptor gene, are estimated to account for 40–60% of a person’s risk of becoming addicted (Blum et al. 2012). Two alleles of the D2 receptor (DRD2) gene exist. Known as A1 and A2, these alleles exist in pairs. This results in three variants of the D2 receptors: A1/A1, A1/A2, and A2/A2. The A2 form of the DRD2 gene is found in two-thirds of the U.S. population, whereas the A1 form is found in one-third. Individuals with the A1 gene have 30–40% fewer D2 receptors.

The presence of the A1 form of the gene has been associated with “reward deficiency syndrome” or “RDS,” a term coined by Blum to describe the reduced dopaminergic state which predisposes individuals to addictions (Blum et al. 1996). Individuals with low DA levels or fewer DA receptors will attempt to raise their DA levels by seeking out substances or activities that increase DA (Blum et al. 2012).

Drugs of abuse (DOA) trigger DA release in the MDP (Adinoff 2004; Pierce and Kumaresan 2006). In fact, they release 2 to 10 times more DA than other pleasurable stimuli (Blum et al. 2012). DA release is believed to be the biochemical basis for the “high” or “rush” associated with the use of DOA and leads to their positive reinforcing effects (Adinoff 2004). Repeated self-administration of DA releasing drugs leads to addiction. Researchers have suggested dopamine release in the MDP may be the final common pathway for the reinforcing effect of all DOA (Pierce and Kumaresan 2006).

Three predominant hypotheses have been proposed to explain DA’s role in the development of addictions. These are hedonia, learning, and incentive salience (Anton et al. 2006; Berridge 2007).

The hedonia hypothesis, also known as the “dopamine depletion hypothesis,” proposes that DA acts as a “pleasure neurotransmitter” in the nucleus accumbens
Hypotheses Regarding Ayahuasca’s Potential Mechanisms

The release of DA is associated with pleasure, whereas DA depletion is associated with anhedonia, or a lack of pleasure. According to this model, DOA initially trigger an elevation in DA resulting in pleasure. However, chronic administration leads to DA depletion, resulting in anhedonia and craving.

The learning hypothesis suggests DA acts to modulate synaptic plasticity, resulting in the reinforcement of reward-related learning (Kelley 2004). This hypothesis will be explored in the next section on the physiological theory of addiction.

The final hypothesis involves “incentive salience.” This hypothesis lists three independent components of reward: liking, learning, and wanting. Dopamine is hypothesized to be responsible for the “wanting” component, also referred to as “incentive salience” (Berridge 2007). Regardless of the model one chooses, the current consensus is that DA release in the MDP is intimately linked with addiction (Adinoff 2004).

Paralleling the dopaminergic neurons in the MDP are neurons that release 5-hydroxytryptamine, also known as 5-HT or serotonin. These serotoninergic neurons originate in the midbrain raphe nuclei and send axonal projections to the VTA, nucleus accumbens, and the prefrontal cortex (Molliver 1987; Steinbusch 1981). DOA cause the release of not only DA, but also 5-HT in the MDP. Chronic administration eventually leads to depletion of these neurotransmitters from presynaptic neurons (Dackis and Gold 1985; Morton 1999).

In the 1990s, Baumann and Rothman at the National Institute of Drug Abuse proposed a “dual deficit model” of addictions based upon these chemical changes. This model theorizes that the repeated self-administration of DOA results in decreased levels of DA and 5-HT. This neurotransmitter deficit is thought to be responsible for the symptoms of withdrawal that occur upon discontinuation of these drugs. Reduced DA levels are hypothesized to contribute to anhedonia and psychomotor slowing, whereas lowered 5-HT levels are believed to contribute to depressed mood, obsessive thoughts, and lack of impulse control. Together, decreased levels of DA and 5-HT are believed to contribute to withdrawal symptoms, drug craving, and relapse (Rothman et al. 2006, 2008).

Biochemical Treatments for Addictions

The MDP is being investigated as a potential target for the treatment of addictions. Two competing models have been proposed to explain how interventions at the level of the MDP might treat addictions. These are known as “antagonist” and “agonist” theories.

The “antagonist model” proposes medicines that block DA release in the MDP will reduce the self-administration of DOA. While antagonist theories are appealing, DA blocking agents have not been demonstrated to be effective in the treatment of addictions (Grabowski et al. 2000, 2004a, b; Kampman et al. 2003).
In fact, DA antagonists, including typical neuroleptics, may actually increase the self-administration of DOA (Carvalho et al. 2009; Matthews et al. 2011).

One possible explanation for this increased use of DOA by individuals who are taking DA blocking medications is a phenomenon known as mesolimbic dopaminergic supersensitivity, or MDS. MDS is thought to be the result of compensatory hypersensitization to dopamine via receptor upregulation following dopamine inhibition or blockade. For example, typical neuroleptics, which exhibit potent D2 blockade, may produce increased sensitivity to dopaminergic stimulation (Carvalho et al. 2009). Medicines that block DA receptors to a lesser degree, such as atypical neuroleptics, have been shown to prevent the development of MDS and are not associated with increased addictive behaviors (Carvalho et al. 2009).

The “agonist model” suggests that medicines which increase DA release in the MDP will reduce craving and withdrawal effects associated with the discontinuation of DOA, thereby reducing repeated self-administration (Rothman et al. 2008). This model employs medicines that are less potent and less addictive than cocaine, methamphetamine, and other DOA to reduce the potential for abuse (Gorelick 1998). Rothman and Baumann refer to this method as “neurochemical normalization therapy” (NNT) (Rothman and Baumann 2003). Evidence supporting NNT comes from a 2005 study (Rothman et al. 2008) in which a nonamphetamine DA/5-HT releasing agent known as PAL-287 was tested to determine its effects on self-administration of cocaine. The researchers found PAL-287 suppressed self-administration of cocaine in Rhesus monkeys (Rothman et al. 2005). Additional support for the agonist model comes from the finding that low doses of DA-releasing medicines, such as amphetamine and phentermine, decrease the self-administration of cocaine (Glowa 1995; Grabowski et al. 2004b; Negus and Mello 2003a, b; Wojnicki et al. 1999). The dopamine agonist bromocryptine has also been shown to reduce craving for cocaine (Dackis and Gold 1985). NNT has been demonstrated to be an effective form of treatment for nicotine dependence (Henningfield 1995; Rollema et al. 2007), opioid dependence (Ling 1994), and alcohol dependence (Gual and Lehert 2001; Overman et al. 2003).

A major challenge associated with the agonist model is that DA agonists can themselves become addictive due to their activation of mesolimbic dopaminergic neurons (Grabowski 2004a; Rothman et al. 2008). High levels of DA are reinforcing. Thus, in order to be an effective treatment for addictions, an agonist must release enough DA to normalize levels, but not so much that it creates reinforcement leading to addiction. One method suggested to reduce the abuse liability of DA agonists is to add a medication with 5-HT agonist properties. Some 5-HT neurons have an inhibitory effect on the release of DA in the MDP and thus attenuate the reward associated with DA agonists (Rothman and Baumann 2006). Evidence supporting the concept that 5-HT agonists counteract the reinforcing effects of DA in the MDP includes the finding that the 5-HT precursor, t-tryptophan, decreases self-administration of cocaine and amphetamine (McGregor et al. 1993; Smith et al. 1986). Also, medications that broadly activate 5-HT systems in the brain reduce self-administration of stimulants and other DOA (Higgins and Fletcher 2003).
Table 7.1 5-HT receptors and their effects upon DA release

<table>
<thead>
<tr>
<th>Receptor site</th>
<th>Agonist/antagonist</th>
<th>Effect on DA in the MDP</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-HT1a</td>
<td>Agonist</td>
<td>Increases release</td>
<td>Stahl (2008), Li et al. (2004), Ichikawa et al. (2001), Alex and Pehek (2007)</td>
</tr>
<tr>
<td>5-HT2a</td>
<td>Agonist</td>
<td>Decreases release</td>
<td>Stahl (2008)</td>
</tr>
<tr>
<td>5-HT2c</td>
<td>Agonist</td>
<td>Increases release</td>
<td>Stahl (2008)</td>
</tr>
<tr>
<td>5-HT2c</td>
<td>Antagonist</td>
<td>Decreases release</td>
<td>Millan et al. (1998), Smith et al. (1998), Alex and Pehek (2007)</td>
</tr>
<tr>
<td>5-HT2c</td>
<td>Antagonist</td>
<td>Increases release</td>
<td>Millan et al. (1998), Alex and Pehek (2007)</td>
</tr>
</tbody>
</table>

Although activation of 5-HT neurons generally reduces DA release, 5-HT agonists exhibit mixed effects on the DA system. 5-HT agonism can either increase or decrease DA release, depending upon the 5-HT receptors involved (see Table 7.1).

Ayahuasca as a Biochemical Treatment for Addiction

Given our understanding of the biochemistry of addiction, an ideal biochemical treatment would provide the following:

- an increase in global serotonin levels
- normalization/stabilization of dopamine in the MDP.

Ayahuasca affects 5-HT in several ways. First, the beta-carbolines in ayahuasca would theoretically raise 5-HT levels via their inhibition of MAO enzymes. Second, as a result of its structural similarity to 5-HT, DMT binds with most, if not all, 5-HT receptors. The actions of DMT on particular 5-HT receptors may play a key role in ayahuasca's effects on DA as well.

As discussed above, dopaminergic surges associated with addictive behavior are thought to underlie, at least in part, the biochemical initiation and reinforcement of a particular reward. In contrast, a relative DA deficit is thought to support addictive behavior, especially the chronic self-administration of DOA. An ideal treatment would normalize and stabilize DA levels in the MDP between the extremes of withdrawal and reinforcement. It would provide levels of DA high enough to attenuate withdrawal, but low enough to avoid further reinforcement of addiction. We propose ayahuasca may achieve this therapeutic biochemical window via multiple opposing mechanisms in what we are dubbing a "tug-of-war" effect. Ayahuasca's effects on DA can be broken down into a dichotomy: mechanisms that raise DA and mechanisms that lower DA in the MDP.

Similar to their effects on 5-HT, the beta-carbolines in ayahuasca block the enzymatic metabolism of catecholamines, which raise global DA levels. In addition to this generalized global increase, harmine has been shown to independently
release DA in the nucleus accumbens shell (Brierley and Davidson 2012). Harmine has also been shown to block DA reuptake into neurons via the DA transporter (DAT) on synaptic membranes (Drucker et al. 1990). Beyond the beta carbolines, DMT’s affinity for 5-HT receptors provides a mechanism for DA elevation in the MDP. DMT increases DA release via agonism at 5-HT1a receptors. Additionally, DMT has recently been found to be an agonist at the trace amine receptor TAAR1. TAAR1 receptors have been shown to modulate dopamine transporters (DAT), blocking the reuptake of DA into neurons, thereby increasing synaptic DA levels (Zhibua and Miller 2007).

DMT’s affinity for 5-HT receptors also results in mechanisms that lower DA in the MDP. Its agonist actions at 5-HT2a and 5-HT2c receptors inhibit DA release. Additionally, DMT has been found to be a sigma-1 receptor agonist. Though the sigma-1 receptor is not well characterized, it is found throughout the limbic system and there is evidence that sigma-1 receptor agonism results in inhibition of DA release (Debonnel 1993; Fontanilla et al. 2009; Navarro et al. 2013). We propose that the net result of these opposing forces on DA efflux in the MDP is the achievement of a therapeutic window between withdrawal and reinforcement. Ayahuasca is thus proposed to have a “normalizing effect” on DA levels in the MDP. These effects of ayahuasca on the DA and 5-HT systems are consistent with other medications that have been explored as potential treatments for addictions based upon NNT.

Biochemical Hypothesis

Ayahuasca exerts anti-addictive properties via its direct and indirect actions on dopaminergic and serotonergic neurons in the mesolimbic pathway. Ayahuasca raises global 5-HT levels attenuating withdrawal effects and mitigating against potential dopaminergic excess when utilizing DA agonists. Ayahuasca balances DA in the MDP between the low levels associated with withdrawal and the elevated levels associated with initiation and reinforcement of addictive behavior. This therapeutic biochemical window is achieved via multiple opposing “tug-of-war” effects on DA.

Physiological Hypothesis of Addictions

The physiologic hypothesis of addictions is based upon a concept known as “neuroplasticity.” Neuroplasticity refers to the ability of neurons to alter their synaptic connections. Such alterations may occur via the formation of new synapses, the elimination of existing synapses, or the remodeling of dendrites and axons (Chklovskii et al. 2004). Addictive drugs have been demonstrated to reorganize neural circuits. Cocaine and amphetamine, for example, have been
demonstrated to produce morphological alterations in dendrites within the nucleus accumbens and prefrontal cortex (Li et al. 2003; Robinson and Kolb 1999). The mechanism responsible for these changes is believed to be altered gene expression in neurons.

Two types of gene regulation are hypothesized to contribute to the development of addictions. These are: (a) up or down regulation of the expression of a gene and (b) a brief burst of gene expression or protein translation. Both types of altered gene expression patterns have been observed in response to the administration of DOA (Berke et al. 1998; Hope et al. 1994).

By triggering the release of DA, DOA activate D1 receptors, which in turn activate cAMP leading to CREB activation (Berke et al. 1998). CREB (cyclic AMP response-element binding protein) is a cellular transcription factor that binds to DNA sequences known as "cyclic AMP response elements" or "CRE." This binding causes an increase or decrease in the translation of numerous genes and alters production of their downstream products including: c-fos, BDNF (Brain-derived neurotrophic factor), tyrosine hydroxylase, and numerous neuropeptides (e.g., somatostatin, endephalin, and corticotropin-releasing hormone) (Purves et al. 2011). DOA influence numerous genes. In fact, chronic cocaine administration has been found to induce more than 100 different genes (Zhang et al. 2005).

Stimulation of the D1 receptor-CREB pathway has been linked to tolerance and dependence with DOA (Hyman et al. 2006). Cocaine and amphetamine stimulate D1 receptors in the nucleus accumbens, which leads to CREB phosphorylation and activation of prodynorphin gene expression (Cole et al. 1995). The dynorphin peptides are then transported to axons of striatal neurons where they inhibit release of DA from terminals of midbrain DA neurons, thus reducing the responsiveness of DA systems (Spanagel et al. 1992; Steiner and Gerfen 1996). D1 receptor-mediated increases in dynorphin can thus be understood as a response to excessive DA in the nucleus accumbens. This increase in dynorphin feeds back to the nucleus accumbens, further reducing DA release (Steiner and Gerfen 1996). Overexpression of CREB in the nucleus accumbens increases prodynorphin gene expression and decreases the rewarding effect of cocaine (Carlezon et al. 1998). Thus, the induction of dynorphin appears to play a role in dependence and withdrawal via a reduction in the responsiveness of DA systems (Koob and Le Moal 1997; Steiner and Gerfen 1996).

In addition to DA, several other neurochemicals are known to influence neuroplastic changes in the context of addiction. BDNF, which is known to play a significant role in neuroplastic changes generally, is thought to play a significant role (Bramham and Messaoudi 2005; Thomas et al. 2009). Glutamate and gamma amino butyric acid (GABA) also play significant roles in the neuroplastic changes associated with addiction (Kalivas 2004).

In the context of addiction, neuroplasticity is thought to underlie what researchers have called "pathological learning" or "diabolical learning." These terms refer to maladaptive learning that occurs when neural mechanisms supporting learning and memory are usurped or "hijacked" by the addiction process.
The hijacked neural learning leads to associations and patterns of behavior that result in repeated self-administration of DOA (Hyman et al. 2006; Stahl 2008).

This maladaptive learning, though pathological in addicts, stems from the evolutionarily advantageous reward-based learning rooted in the biological drive for survival and reproduction. This drive leads individuals to search for natural resources and that are necessary for survival and reproduction such as food, shelter, and sex. The behaviors leading to the procurement of these resources are positively reinforced (i.e., they are rewarded) by the release of dopamine in the MDP. This positive reinforcement leads to these behaviors being learned (i.e., they persist and increase over time). With time and repetition, these behaviors become automatized.

As previously stated, DOA trigger DA release in the MDP. However, there is a quantitative difference in the intensity and longevity of dopaminergic activity with DOA relative to natural rewards. DOA release DA in much greater amounts and for longer periods of time than most natural stimuli (Hyman et al. 2006). This accentuated release of DA in the “reward pathway” has been proposed to reinforce behaviors designed to obtain more addictive drugs (Koob and Bloom 1998). Thus, the biochemical effects of DOA result in the transformation of an important beneficial brain circuit into a dysfunctional, maladaptive one.

The automatized reinforcement of addictive behavior with DOA can also lead to sensitization of the MDP to formerly neutral stimuli. These stimuli, once conditioned, reinforced, and “learned,” become sources of dopaminergic elevations that may lead to drug use, relapse, and craving. For example, a heroin addict will learn to associate a particular street corner, spoons, needles, the color of a couch, or a particular time of day with his drug use. Exposure to these stimuli results in elevations in DA that prime the MDP and associated neurological processes, leading to further addictive behavior and reinforcement. Thus, the system has been “hijacked.”

While early theories suggested that pleasure or reward associated with the release of DA in the MDP was responsible for the repeated use of DOA, subsequent studies have revealed the role of DA in the MDP to be significantly more complex and nuanced (Adinoff 2004). As noted earlier, there are multiple competing hypotheses. Rather than merely acting as a hedonic (i.e., pleasure producing) signal, DA has been suggested to promote reward-related learning as well (Hyman et al. 2006).

**Physiological Effects of Ayahuasca**

Ayahuasca acts on many neurochemicals known to be associated with brain plasticity. By acting on these chemicals and their associated pathways, cascades, and related processes, ayahuasca may facilitate adaptive neural architectural changes. These changes may then facilitate the breakdown of pathological associations, triggers, cues, and patterns of behavior associated with addiction.
Neurophysiologic changes can thus facilitate a "rewiring" of the "hijacked" reward pathway within the brain.

Harmine, the predominant beta carboline in ayahuasca, stimulates DA release in the nucleus accumbens (Brierley and Davidson 2012). DMT acts as an agonist at several 5-HT sub receptor types, which also triggers DA release. Harmine also increases levels of BDNF (Osorio et al. 2011). Though not yet well understood, ayahuasca also has effects on gabaminergic and glutamaturgic systems, both of which are heavily implicated in neuroplastic changes (Ciranna 2006; Li et al. 2011). These biochemical effects trigger alterations in the expression of genes that revise the communicative architecture between neurons. These neuroplastic changes are thought to correlate with changes in learned behavior. Thus, old maladaptive circuits may be altered under the influence of ayahuasca to new adaptive circuits, where pathological associations no longer control behavior.

**Physiological Hypothesis**

Ayahuasca triggers the release of DA in the nucleus accumbens, which stimulates D1 receptors leading to altered gene expression. The products resulting from these altered gene expression patterns trigger neuroplastic changes that reduce self-administration of addictive drugs. In addition to DA, ayahuasca exerts effects on other neurochemicals that have been implicated in neuroplastic changes in the context of addiction, including glutamate, GABA, and BDNF.

**Psychological Theory of Addiction**

A psychological model of addictions is based upon the finding from the 1950s and 1960s that the administration of lysergic acid diethylamide (LSD) decreased alcohol consumption in chronic alcoholics. Initially, researchers investigated LSD's purported ability to produce psychosis, a concept known as the "model psychosis" concept (Hoffer and Osmond 1967; Hoffman 2009). Subsequently, however, researchers theorized LSD's effects were more similar to alcohol withdrawal symptoms than psychosis, leading them to postulate LSD might produce an experience similar to delirium tremens. They hoped LSD would induce a "hitting bottom experience," thereby deterring alcoholics from drinking (Hoffer and Osmond 1967).

In 1953, Osmond and Hoffer conducted a study examining LSD's potential benefits as a treatment for alcoholism. They selected 24 alcoholics from the inpatient unit at the University Hospital in Saskatoon, Canada. These individuals, who had failed every available treatment and were viewed as having a very poor prognosis by their therapists, were administered a single dose of LSD. The results demonstrated 12 (50 %) subjects were "unchanged," 6 (25 %) were "improved," and 6 (25 %) were "much improved" (Smith 1958).
The positive findings of this study generated interest among other researchers who set out to explore LSD as a potential treatment for alcoholism. Results from early studies were so encouraging that by the late 1960s, six alcoholism treatment programs in North America were employing LSD in their treatment model (Ruck et al. 1979). Eventually, two distinct types of therapy evolved utilizing LSD as a treatment for addictions. These were known as "psycholytic therapy" and "psychedelic therapy."

Psycholytic therapy grew out of researchers' observations that LSD's effects were often very different from those predicted by the "model psychosis" concept. Rather than becoming paranoid or guarded during LSD sessions, subjects were noted to talk more freely about their problems. They also exhibited increased insight into the emotional meaning of symptoms, improvements in depression, reduced anxiety, reduced compulsions, increased sense of well being, and increased access to previously repressed memories (Hoffer and Osmond 1967; Hoffman 2009). These discoveries generated interest in the possibility of integrating LSD into psychotherapy.

The term "psycholytic" comes from the Greek roots psyche meaning "soul" or "personality" and lysis, meaning "dissolution" (Merriam-Webster, n. d.). Psycholytic therapy was reported to dissolve psychic conflicts and release emotional tension (Grof 2009). Utilized more frequently in Europe than North America, this method involved the administration of relatively low doses of LSD at one- to two-week intervals for 15-100 sessions.

**Psychological Effects of Ayahuasca**

Similar to psychedelic medicines such as LSD, the effects of ayahuasca are highly dependent upon the set and setting in which it is used. The term "set" refers to "the attitude of the person at the time of use, including his personality structure" whereas "setting" refers to "the influence of the physical and social setting within which the use occurs" (Zinberg 1984). Despite the highly variable set and setting in which ayahuasca is being used today, certain common features of the ayahuasca experience have been observed.

Psychologist Shannon (2002), who performed one of the most in-depth studies of ayahuasca's effects, described the following changes following ingestion of ayahuasca:

1. Alterations in thinking: Changes in concentration, attention, memory, judgment, and reflective awareness.
2. Altered sense of time: The rate by which time passes may appear to accelerate or decelerate. The duration of time may be experienced as infinite or infinitesimal. Feelings of timeless or existing outside time may be experienced as well.
3. Fear of loss of control: A fear of losing control of reality. If cultural conditioning has resulted in positive expectations and a clear understanding of the experience, mystical, and transcendent states may ensue.
4. Changes in emotional expression: Heightened emotional reactivity may range from ecstasy to despair.

5. Changes in body image: Boundaries between the self and others may dissolve including feelings of depersonalization, derealization, and cosmic unity.

6. Perceptual alterations: Visual imagery and hallucinations are prominent and hyper-acuteness of sensory perception may occur. Individual and cultural expectations may influence the content of perceptual alterations.

7. Changes in meaning or significance: Feelings of heightened insight or profound meaning.

8. Sense of the Ineffable: The experience may be difficult or impossible to communicate to others.


10. Hypersuggestibility: Increased susceptibility to verbal and nonverbal cues is characteristic of the altered state experience. The ordinary filtering mechanisms that allow individuals to discriminate between various forms of input may be temporarily suspended.

Grob at Harbor-UCLA Medical Center reported these same 10 characteristics are "virtually universal" to altered states of consciousness (2006). Shannon reported these changes might produce psychological benefits resulting from the experience of positive affects and enhanced reflection and insight (see Shannon, this volume). Grob et al. (1996) studied the effects of ayahuasca in members of a Brazilian ayahuasca religion, the União do Vegetal (UDV), who regularly ingest ayahuasca as part of their religious ceremony. He found these individuals scored higher on neuropsychological testing than controls who had never drunk ayahuasca. Grob concluded, "the long-term consumption of ayahuasca within the structured UDV ceremonial setting does not appear to exert a deleterious effect on neuropsychological function" (p. 93).

Reports pertaining to ayahuasca's psychological and neuropsychological effects suggest two possible explanations that may help explain ayahuasca's psychological benefits in the treatment of addictions. One explanation suggests ayahuasca facilitates access to important conscious and unconscious memories, allowing the release of repressed emotions and catalyzing the healing of unresolved traumas. This results in individuals being freed from habitual, dysfunctional patterns of addiction. This explanation is based upon the psychodynamic model, which is similar to the psycholytic theory of addiction treatment.

A second explanation suggests ayahuasca allows individuals to observe and experience the past, present, and potential future outcomes of their choices. By witnessing the outcomes of the continued use of addictive substances as well as the outcomes of abstinence from these substances, individuals acquire a more complete understanding of the consequences of their decisions. This allows them to make better choices and to stop using addictive drugs (R. Yamberla, personal communication, March 25, 2013). These two explanations are not mutually exclusive, but in fact may be complementary.
Psychological Hypothesis

Ayahuasca treats addictions by facilitating access to important conscious and unconscious memories, allowing for the release of repressed emotions, and catalyzing the healing of unresolved traumas. Ayahuasca also provides increased insight and understanding of the past, present, and future outcomes of choices that contribute to addictive behaviors. This perspective allows for improved decision making. These effects result in psychological freedom from the habitual, dysfunctional patterns associated with addiction.

Transcendent Theory of Addictions

An alternative to the psycholytic model was the "psychedelic model" of treatment. Hoffer and Osmond developed this model during their research exploring LSD's potential as a treatment for alcoholism. "Psychedelic therapy" involved the administration of relatively high doses of LSD over one to three sessions (Hoffer and Osmond 1967). The goal of this type of therapy was to induce a "psychedelic peak experience," a concept modeled after Maslow's "peak experience" (Grinspoon and Bakalar 1997).

Grof (2008) defined a "psychedelic peak experience" as:

An ecstatic state, characterized by the loss of boundaries between the subject and the objective world, with ensuing feelings of unity with other people, nature, the entire Universe, and God. In most instances this experience is contentless and is accompanied by visions of brilliant white or golden light, rainbow spectra or elaborate designs resembling peacock feathers. It can, however, be associated with archetypal figurative visions of deities or divine personages from various cultural frameworks.

Harvard professor Grinspoon (1997) explained the primary goal of psychedelic therapy was the induction of a mystical experience that would change the way individuals see themselves and the world. Researchers viewed psychedelic peak experiences as profound experiences that catalyzed recovery from addictions.

In a study published in 1970, Pahnke investigated whether alcoholic patients who experienced a "psychedelic-peak experience" improved more than patients who did not. He found a statistically significant \( p < 0.05 \) improvement at 6-month follow-up in individuals who had a peak experience compared with individuals who did not.

Further evidence supporting the notion that transcendent experiences catalyze improvements in addictions comes from anecdotal sources. For example, William Griffith Wilson described a transcendent experience that turned the tide in his struggle with alcoholism. While hospitalized, Wilson hit bottom. As he later explained, what happened next would change his life forever:

Lying there in conflict, I dropped into black depression. Momentarily my prideful obstinacy was crushed. I cried out, "Now I'm ready to do anything... If there be a God, will he..."
show himself!" The result was instant, electric, beyond description. The place lit up, blinding white. I knew only ecstasy and seemed on a mountain. A great wind blew, enveloping and permeating me. It was not of air, but of Spirit. Blazing, came the tremendous thought, "You are a free man!" Then ecstasy subsided. Still on the bed, I was now in another world of consciousness, which was suffused by a Presence. One with the Universe, a great peace stole over me and I thought, "So this is the God of the preachers, this is the Great Reality." But reason returned, my modern education took over. Obviously I had gone crazy. I became terribly frightened (W. W. 1994).

After this experience, Wilson never drank alcohol again. Based upon his own personal experience, he believed the key to overcoming addictions was to have a spiritual or transcendent experience (W. W. 1994). Today, the founder of Alcoholics Anonymous is better known as Bill W.

**Transcendent Effects of Ayahuasca**

Similar to LSD, psilocybin, and other psychedelics, ayahuasca has been reported to induce transcendent, mystical, or peak experiences (Shanon 2002). Stace (1961) described the following seven characteristics of mystical experiences:

1. **Unity**: Feelings of oneness behind the multiplicity in the world or a dissipation of one's boundaries resulting in feelings of becoming one with an existence larger than one's self
2. **Transcendence of time and space**
3. **Noesis**: Direct, intuitive knowledge
4. **Positive feelings of blessedness, joy, peace, and happiness**
5. **A sense of sacredness**
6. **Paradoxicality**: Seeming dualities are transcended such that a unitive whole is experienced
7. **Ineffability**: Experiences cannot be defined with words.

Each of these characteristics has been reported to occur in association with ayahuasca use (Shanon 2002).

Ayahuasca has also been reported by others to produce transcendent experiences. Kjellgren et al. (2009) obtained questionnaires from 25 northern Europeans who had ingested ayahuasca between 1 and 70 times each. These individuals described six themes related to their ayahuasca experiences. One of these themes involved a shift from a frightening state to a state that is "limitless, omnipotent, and indescribable" (p. 312). A second theme involved reports of transpersonal experiences including encounters with a spirit world, changes in time and space, and experiences of their own death. A third theme involved changes in worldview, personal development, interests, and healing effects. These included greater self-awareness and a sense of being more present. Subjects also described feeling more love toward others and themselves. Negative psychological patterns were reported to decrease or stop (p. 313).
Trichter et al. examined changes in spirituality among 49 individuals who participated in ayahuasca ceremonies for the first time (2009). Utilizing the Peak Experience Profile (PEP), the Spiritual Well Being (SWB) scale, and Hood’s Mysticism Scale (M Scale), they found more than 75% of participants reported their ayahuasca experience impacted their spiritual beliefs, and over 75% reported an increased interest in spiritual practices following their ayahuasca experience (p. 131).

**Transcendent Hypothesis**

Ayahuasca treats addictions by facilitating transcendent or peak experiences. These experiences produce changes in belief systems, personal values, and worldviews that reduce the use of addictive substances.

**Summary**

Drug addiction is a worldwide problem with high rates of morbidity and mortality, enormous social ramifications, and tremendous negative economic impacts. Existing pharmacological treatments offer only modest improvements in abstinence and remission rates, leaving a great need for new medicines that can more effectively treat addictions.

Ayahuasca is a plant-derived medicine with an extensive history of therapeutic use among indigenous cultures throughout the Amazon River Basin. Ayahuasca’s potential benefits as a medicine and as a treatment for addictions remain largely uninvestigated by Western-trained physicians and scientists. Recently, studies have been initiated examining ayahuasca’s effectiveness as a treatment for addictions. However, the mechanisms by which ayahuasca exerts its anti-addictive properties remain unknown.

We have proposed four unique yet interrelated hypotheses regarding ayahuasca’s potential mechanisms of action in the treatment for addictions. We strongly encourage the reader to view these four hypotheses as distinct yet interdependent. Rather than focusing solely on one level, we believe it is important to recognize and utilize multiple levels of understanding and intervention in order to more fully comprehend the effectiveness of this medicine and to develop more effective treatments for addictions.

Previous studies indicate that ayahuasca can be safe and effective when used in a therapeutic setting. Additional research is needed to better understand and maximize ayahuasca’s effectiveness as a treatment for addictions. Researchers will need to take into account the importance of set and setting when carrying out research studies. The belief system of the researcher as well as the individual utilizing ayahuasca may influence the experience resulting from ayahuasca
ingestion. Furthermore, the physical and social context in which ayahuasca is utilized may affect the outcomes of ayahuasca use.

It is our hope that future research will involve collaboration with indigenous healers whose extensive experience and knowledge of ayahuasca may add significantly to our understanding of this medicine. Such collaboration has been woefully lacking in the past due to a variety of factors including: (a) cultural and language differences, (b) mistrust of outsiders due to a history of persecution for utilizing traditional healing methodologies, and (c) discounting the value of what indigenous healers have to offer. We must learn to appreciate and value the knowledge and experience of indigenous healers if we ever hope to learn from them. Acknowledging the experience and knowledge possessed by indigenous healers may help us to better understand the benefits of ayahuasca, as well as open doors to yet-unknown treatments for addictions.

References


Hypotheses Regarding Ayahuasca's Potential Mechanisms


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