INTRODUCTION

For thousands of years, human beings have used medicinal plants to enhance their health and well-being. In cultures around the world, plants commonly referred to as psychedelic, hallucinogens, and entheogens have played central roles in their healing practices. These vision-inducing plants have also played important roles in the religious and spiritual practices of many societies, evoking powerful emotional, cognitive, and therapeutic reactions. These plants that were central to concepts of health, spirituality, and well-being were, however, demonized and rejected by European cultural institutions in the process of the development of the modern world. Their legacy was largely lost to Western civilization until anthropology recovered this knowledge, and it was re-embraced by some in the context of the social revolutions of the 1960s. This convergence of politics and foreign ethnomedicines provoked oppressive reactions, leading to a virtual ban on the use of these powerful medicines in research and therapy.

This introduction has several purposes:

1. to situate these plants in a social context that explains the divergent perspectives on these substances;
2. to provide a general understanding of the premodern perspectives regarding the uses of these substances as medicines;

3. to explain our use of *psychedelic*, as opposed to *hallucinogen* and other terms, to refer to these substances and their effects; and

4. to illustrate the neurological bases of the effects of psychedelic substances as *psychointegrators* (as discussed below).

Psychedelic plants constitute part of humanity’s ethnobotanical knowledge of substances of great medicinal and therapeutic importance cross-culturally and throughout history. Where used, these substances generally have been viewed as central sources of spiritual experience and religious participation, providing inspiration for the institutionalization of religious sentiments and activities (e.g., see La Barre 1972; Schultes and Hofmann 1979; Dobkin de Rios 1984; Winkelman and Andritzky 1996; Schultes and Winkelman 1996; Rätsch 2005). These plants are also considered the most powerful of medicines, central to the cultures’ healing traditions. These plants are important in understanding cultural and religious development as well as, perhaps, the evolution of humans’ “wet ware”—the neurochemical transmitter systems of our brains.

**Societal Differences in the Use of Psychedelic Plants**

Cultural use of psychedelic plants is not universal but varies as a function of social conditions. Different types of societies make different assessments of their value and potentials. These differences in their use are reflected in the dramatically larger number of psychedelic plants used in the New World in comparison to the Old World cultures (La Barre 1970). These differences have been attributed to cultural factors because there are psychedelic plants present but not used for religious purposes in the Old World (e.g., Europe) (La Barre 1970; Furst 1972; Schultes and Hofmann 1979), where they were often associated with witchcraft (Harner 1973). Institutional political factors are also responsible for the lack of use of these psychointegrator plants. Hallucinogenic plant use is not typically institutionalized in complex societies (Dobkin de Rios and Smith 1977; Winkelman 1991). Cross-cultural analyses reveal that increasing social and political complexity, particularly political integration, leads to reduction in the use of psychointegrator plants (Winkelman 1991). This negative relation to political integration reflects the dynamics of their psychocognitive effects and their inherent conflicts with the psychosocial needs of hierarchical societies.

The repression of and restrictions on use of psychedelics as a function of increasing political integration reflect their typical patterns of use and their effects on social relations and personal interpretations of the world. Dobkin de Rios and Smith (1977) suggest that these plants are typically repressed in state-level societies because they constitute a potential threat to the religious interpretations of those who hold social and religious power. Psychedelic medicines are
typically employed in social settings where local idiosyncratic interpretations derived from the set and setting (personal expectations and the local situational influences) play powerful roles in shaping the experiences. Local interpretation of the experiences could pose a threat to the centralized hierarchical control of religious consciousness and political authority, thus undermining social control. Such conflicts could be expected, given the typical cross-cultural patterns of use of these plants in small group community settings, where they enhance group cohesion and reaffirm traditional value orientations and cosmological beliefs. They consequently reinforce a traditional community-based mythos and social order rather than interpretations of hierarchical political orders and their ideologies of control.

The social contexts associated with the use of psychedelics illustrate their applications to facilitate adaptations to social change. Under conditions of rapid social change, they facilitate adjustments to changing circumstances by enhancing the mediation between conceptual systems (e.g., see Andritzky 1989). The widespread use of the *Banisteriopsis* genus (*ayahuasca*) in Amazonia in collective rituals assists group identity formation and management of acculturation problems by mediating between the indigenous world view and the European-derived systems (Andritzky 1989). The symbolic synthesis of traditional and new beliefs provoked by the use of these plants facilitates psychosocial adjustment. A similar dynamics of psychosocial adjustment was noted in the selective adoption of the Peyote Religion (Native American Church) among the Navajo (Aberle 1966). The early Navajo adherents were primarily those who experienced the greatest relative loss from federally imposed livestock reduction programs. The Native American Church provided a community ethos that reinforced orientations to traditional values of community solidarity and facilitated an adjustment of the Navajo values of collectivism to the broader society’s emphasis on individualism. The burgeoning use of psychedelics in American culture was also associated with periods of rapid social change in the United States (i.e., 1960s and 1990s). There is, however, a more primordial pattern of use of psychedelic medicines.

**Cross-Cultural Uses of Psychointegrators**

In cultures around the world that use psychedelic plants, they are consistently associated with the fundamental principles reflected in the etymology of the term *entheogens*—generating the experience of the god within—reflecting the belief that these plants are powerful spiritual sacraments that provide access to sacred worlds. These sacred substances also have simultaneous therapeutic applications (see Embodden 1972; Furst 1972, 1976; Schultes and Hofmann 1979; Wasson et al. 1986; Dobkin de Rios 1984; Schultes and Winkelman 1996; Winkelman and Andritzky 1996; Rätsch 2005). As the authors in the present volumes show, these uses are dramatically expanded as their medical potentials are discovered in the context of the diseases and illness of the modern world.
In the premodern world, psychedelics were revered for their ability to dramatically alter experience, shifting self-awareness to an “other-worldly” sacred or spiritual domain. This spiritual encounter was seen as having important applications as a therapeutic event. Indeed, the plants themselves were viewed as animistic agents, providing the basis for personal relations with an animistic world, especially power animals. The experiences they induced provided the opportunity for participation in a mythical time which was the origins of cultural values and religious beliefs. This direct contact with a spiritual source of power was related to self-identification and ego transformation. The use of these substances was focused on healing and divination, and for enhancement of social solidarity and interpersonal and community relations and for strengthening social identity and group cohesion (Dobkin de Rios 1984; Winkelman 1996a).

The worldwide interpretations of these substances emphasize their simultaneous religious, spiritual, and medicinal roles. McKenna (1992) documents the worldwide prehistoric practices of using mushrooms as a central part of a cultural ethos relating to the earth and mysteries of nature. He contends that the mushrooms enhanced self-awareness and a sense of contact with a “Transcendent Other.” This reflected an experience of the sentience and intelligence of nature, an intimate awareness of our interconnectedness with nature, the earth, and the universe. McKenna proposed that entheogenic substances played an important role in the evolution of human consciousness, producing a sense of interconnectedness and balance with nature.

Psychedelic medicines were central to many shamanic practices, raising the question of whether they were the progenitors of humanity’s original spiritual practices. The prehistorical role of vision-inducing plants as progenitors of religion was suggested by La Barre (1972), who called attention to their potentials to stimulate the visionary and supernatural experiences which often give rise to religious traditions. He suggested that these substances stimulate aspects of the subconscious mind, represented as supernatural beings and spiritual beliefs, reflecting the subjective world of human experience, perception, and consciousness. In essence, the cross-cultural patterns of the use of psychedelics indicate that they are functionally related to the origins of religion, consciousness, and perhaps ultimately modern human consciousness. Why should these plants have such central roles in human consciousness and culture? The answer lies in their neurological effects that produce an integration of various psychophysiological processes, a biologically driven psychointegration.

**Neurophenomenological Approaches: Psychedelics as “Psychointegrators”**

Explaining the institutionalized use of psychedelic plants requires integration of interdisciplinary, cross-cultural, and neurophenomenological perspectives to provide understandings of: 1) their cross-cultural similarities in terms of biochemical mechanisms and 2) their psychodynamic effects on human experience.
The cross-cultural similarities in the experiences and interpretations of these substances suggest similar psychophysiological properties of the diverse psychedelic plants. Neurophysiological studies illustrate their common physiological effects produced through intervention in the serotonergic neurotransmitter systems. An interdisciplinary synthesis (Winkelman 1996a, 2001) provides the rationale for the term “psychointegrator” to refer to the central effects of these substances, explaining their cross-cultural social and therapeutic uses in terms of effects on the serotonergic neurotransmitter systems.

The role of serotonin as a “neuromodulator,” the structural similarity of psychedelics and serotonin, and the specific effects of the psychedelics on serotonergic transmission are the bases for their characterizations as “psychointegrators.” Psychointegrators enhance integration of information through stimulating areas of the brain central to managing processes related to fundamental aspects of self, emotions, memories, and attachments. These processes are necessary for the overall integration of information in the brain. This psychointegrative effect is manifested physiologically in the typical effects on brain waves produced by these substances, the stimulation of coherent theta wave synchronization along the neuraxis, the nerve bundle linking the structural levels of the brain. It is manifested psychologically in the experiences of healing, wholeness, interconnectedness, cosmic consciousness, and other transpersonal experiences which these substances regularly produce (e.g., see Grof 1975, 1980, 1989, 1992; also Volume II here).

Psychointegration underlies the psychedelics’ cross-cultural use as sacred and therapeutic agents. The effects of psychointegrators upon neural, sensory, emotional, and cognitive processes illustrate their adaptive advantages produced by the stimulation of the serotonergic systems. This involves an enhancement of consciousness provoked by increasing the integrative information processing, achieved by activation of the serotonergic circuitry between the lower structures of the brain (R-complex and paleomammalian brain; MacLean 1990). Psychointegrative effects derive from the disinhibition of emotional and social processes and the stimulation of systemic integration of brain functions, particularly the integration of limbic system emotional processes with the neocortical processes. Psychointegrators couple nonlinguistic behavioral and social–emotional dynamics with rational processes and functionally integrate different systems of the brain. Psychointegration produces spiritual and transcendent experiences by enhancing operations of basic structures and functions of consciousness (self, other, and affect/attachment) (Winkelman 2003).

These neurological foundations help explain the widespread common patterns of use of these plant substances in religious and therapeutic practices. Psychedelic plants are generally used along with other means of inducing ASC (altered states of consciousness) in shamanistic healing practices that reflect the nearly universal institutionalization of the psychobiological potentials of ASC (Winkelman 1986a,b, 1990, 1992). Through a number of physiological and psychological mechanisms, the ASCs they produce result in physiological changes that facilitate healing and cognition (Winkelman 1992, 2000).
These psychedelic-induced alterations of consciousness are a quintessential spiritual experience of “ecstasy,” providing a neurological basis for the role of chemical agents as sources of spiritual experience and personal transformations.

Why Psychedelic Medicines? Hallucinogens, Entheogens, and Psychointegrators

The use of the term psychedelic to refer to these medicines and their effects reflects a careful consideration of many perspectives, including botanical, medical, and social. Other frequently employed terms which are similar, but not synonymous, include psychotomimetic, hallucinogen, holotropic, entheogen, and more recently, psychointegrator. All of these, including psychedelic, have limitations. We have chosen to use psychedelic for its currency, but not without reservations.

HALLUCINOGENS

Cross-cultural commonalities in the experiences induced by the diverse substances called hallucinogens do not derive from a common botanical family; the diverse plants and substances that produce these effects occur in nearly 100 species and a wide range of genera and families (Schultes and Hofmann 1979; Rätsch 2005). The classic characterization of these substances as hallucinogens was based on subjective criteria, their ability to produce visions, voices, thoughts, and alterations of perceptions and mood in nontoxic doses (Siegel 1984). This subjective basis for the classification of these substances as hallucinogens therefore reflected cultural interpretations emphasizing a medical definition of hallucinations as false and disturbances of thought and/or experiences without a real basis. Similarly, the early psychiatric term psychomimetic—psychosis mimicking—implies a psychotic and delusional basis for the experiences, ignoring their central phenomenological aspects of these experiences as representing transcendent truths, realities with greater veridicality than our ordinary real reality experiences. Cross-culturally, these substances are interpreted as invoking perceptions of a spiritual realm, an important source of valid information, in direct contrast with the implications of delusions emphasized by these other terms.

Recognition of the shortcomings of these medical terms prompted the development of new terminology. The term psychedelic, referring to the extraordinary conceptual (mind-manifesting) impact upon human experience and understandings, was developed in the context of LSD (lysergic acid diethylamide) experiences and the social movements with which they were associated. Consequently, there are general connotations associated with the term psychedelic derived from these counter-cultural social movements. This has politicized the term psychedelic and consequently made it undesirable to many. The focus on the mental also fails to capture the significant emotional and therapeutic experiences associated with these substances.
ENTHEOGENS

Schultes and Hofmann (1979) referred to these substances as “plants of the gods,” reflecting the indigenous terms for these plants found around the world and the perceptions of these plants as having indwelling spiritual influences. In light of these widespread characterizations, Ruck et al. (1979) coined the term entheogens from the Greek entheos, referring to “the god within,” and gen, “action of becoming.” While reflecting many cultural perceptions of these substances, the concept of entheogen does not reflect other personal and cognitive dynamics of these plants’ effects. Furthermore, entheogen implies a spiritual basis that may alienate a more scientific approach to the study of these substances.

PSYCHointegrators

Winkelman (1996a, 2001) introduced the term psychointegrators as reflecting both neurological and experiential effects of these substances. The cross-cultural perceptions regarding the effects of these substances coincide with the principles of their action based on neurobiological research, providing a neurophenomenological perspective that integrates neurological and experiential effects (Winkelman 1996b). Psyche reflects not only the mind but also the soul and spirit, the broader bases to which psyche once referred. Psychointegrator implies the stimulation of the mind, emotions, body soul, and spirit to integrative development. Psychointegration involves a stimulation of both mental and emotional processes through a physiological dynamic that forces the organism toward an integrative holistic growth state in the integration of the soul, mind, and spirit for growth and development. This model of psychointegration is extended in Vollenweider’s (1998) research of their effects on the corticostrato-thalamocortical loops linking the sensory gating systems of the lower brain and the receptor areas of the frontal brain. These same meanings are inherent in the term holotropic proposed by Grof (1975, 1989; also see Volume II here) to describe the psychodynamic actions of these substances in promoting an orientation toward wholeness.

The neurotransmitter effects of psychointegrators on the serotonergic neurotransmitter system involve a number of psychointegrative effects. These begin with neurotransmitter processes, and continue through effects on neural circuitry, functional systems of the brain, and consequently emotional, cognitive, and psychological processes. These together produce systemic macro-level integrative effects across hierarchical levels of the brain (e.g., the enhanced connections between the R-complex and limbic brain) (Winkelman 1996a) and across functional systems (Vollenweider 1998). These psychointegrative effects are epitomized by their stimulation of the functions of the serotonergic neurotransmitter system, a “neuromodulatory” system which integrates diverse forms of information and systemic demands of the body, modulating the activities of dozens of bodily and brain processes, including the other neurotransmitter systems.
The psychointegrators are by necessity also “disintegrators”—the connection with all comes as a consequence of disintegration of the ego. Some of these effects result from their powerful “de-conditioning” influences, where they inhibit conditional responses and block habitual neurotransmitter pathways. Their effects are also extremely dissociative, engaging in some systems to the exclusion of others—such as the external environment. Their dissociation reflects the extreme activation of other kinds of connections that totally occupy consciousness.

In spite of the greater accuracy of the term psychointegrator, we have nonetheless decided to use the term psychedelic for the title to these volumes and accept our authors’ use of other terms such as hallucinogen and entheogen. The use of psychedelic is in part practical, given its greater acceptance, currency, and widespread recognition. Psychedelic (mind-manifesting) is also political, a reminder to use our minds, in response to the stifling political climate which has until recently precluded the effective investigation and therapeutic use of these important medicines. Psychedelic was coined in a context in which its political dimensions soon became obvious to supporters and detractors. As our conclusions to this volume indicate, we think that in addition to scientific, religious, and even business approaches, political approaches are also necessary to reform well-intentioned but misguided governmental policies and administrative decisions that precluded access to these substances for research and therapeutic purposes for too many years. These two volumes indicate that a realistic, evidence-based approach is making headway.

NEUROLOGICAL PERSPECTIVES ON PSYCHOINTEGRATORS

The effects of psychedelics on neurotransmission are responsible for the principal aspects of the associated physical, emotional, cognitive, and sacred experiences and their therapeutic applications. The model of psychointegration presented here is not the finding of a single study but represents an integration of many studies and the generalizations regarding the effects of psychedelics that have developed over decades of research. The effects of the psychedelics on neurotransmission are among the best understood effects of drugs on neurotransmission (Mandell 1985). Since the 1960s, it has been recognized that the major substances labeled as psychedelics (hallucinogens such as LSD, mescaline, and psilocybin) have common effects on the serotonergic neurotransmitters. Laboratory studies of LSD effects provide diverse findings as a consequence of differences derived from varying procedures and dosages, as well as distinct phase effects and the consequences of set and setting (Freedman 1984). Most psychedelics (e.g., indoleamines, such as psilocybin and LSD, and the phenethylamines, such as mescaline and tetrahydrocannabinols) have effects that generalize to one another, reflecting similar neurochemical mechanisms of action and global properties involving effects upon serotonin pathways and mechanisms (Aghajanian 1994; also see Vollenweider 1998).
Similar effects on serotonin mechanisms are produced by LSD and lysergic acid amide (found naturally in morning glories), psilocybin (from mushrooms of the genera *Psilocybe, Conocybe, Paneolis*, and *Stropharia*), harmine and harmaline of the genus *Banisteriopsis*, and DMT (dimethyltryptamine) and similar substances from the *Virola* genus and species of *Anadenanthera*. Mescaline (from peyote) and similar synthetic drugs (STP, DMA, MDA, and MMDA) and myristicin and elemicin from the genus *Myristica* (e.g., nutmeg) more resemble norepinephrine but have end effects similar to those of the LSD-like substances [but see Passie this volume and Frei et al. (2001) for distinct mechanisms and EEG effects of MDMA]. These substances’ effects on sensory, behavioral, emotional, cognitive, and psychodynamic experiences and processing involve integrative effects on information processing, providing the rationale for their characterization as psychointegrators (Winkelman 1996a, 2001).

A basic systemic effect of psychointegrators involves induction of serotonergic-mediated discharge patterns from the limbic or paleomammalian brain that result in enhanced connections and coordination across the levels of the brain. This is reflected in a general increase in the coherence of the brain waves, their limbic-frontal cortex integration, and the interhemispheric synchronization of the two cerebral hemispheres (left brain–right brain) of the frontal cortex (Mandell 1980, 1985; Winkelman 1996a). The serotonergic action of the LSD-like psychedelics integrates brain functioning from neurophysiological through cognitive levels, stimulating an integration of pre-linguistic social, emotional, and behavioral processes with the frontal cortex’s linguistic and egoic functions.

The therapeutic effects of psychointegrators derive from the activation of emotional and personal processes coordinated in the limbic system and paleomammalian brain, which underlie personal identity, attachment and social bonding, emotion, and conviction in beliefs. Psychointegrators stimulate the integration of the brain’s behavioral and social–emotional processing output into the frontal cortex’s language-based ratiomentation, egoic representations, and personal identity. These biochemically based physiological effects may produce awareness of repressed memories, integration of emotional and rational processes, and resolution of conflicts through integration of the processes of the different functional systems of the brain. The systemic integrative effects of these substances begin with their action at neurotransmitter levels, providing a rationale for using the term *psychointegrator* to refer to their effects.

**Psychointegrators and Neurotransmitter Functions and the Brain**

Neurotransmitters act through a number of mechanisms, exercising both inhibitory and excitatory effects (blocking and facilitating) in modulating the effects of other neurotransmitters. Psychedelics have these roles in the serotonergic system’s receptor sites sometimes as agonists, and in other sites as antagonists.
(or blockers) thus preventing the normal responses of a receptor. These effects on neurotransmission mediate their profound effects on human consciousness (for sources, see note 2). Psychointegration derives from a range of effects on brain transmission. Because of the diverse types and functions of serotonin and the diverse actions of the psychointegrators, there are various kinds of interactions between the two, including interference with serotonin reuptake, activating serotonin receptor sites, and blocking the action of serotonin on its usual neurotransmitters sites.

Mandell (1980) first proposed that common neurobiochemical pathways of psychedelic and other transcendental experiences involve a biogenic amine–temporal lobe interaction manifested in high-voltage slow wave EEG activity originating in the hippocampal–septal area of the limbic system. This limbic system discharge pattern reflects the activation of serotonergic connections with lower brain structures, engaging a circuitry that produces strong theta wave discharges. These discharges ascend the neuraxis, the major ascending nerve bundles of brain, producing an integration of limbic processes in the frontal cortex and an interhemispheric synchronization and coherence between the two frontal hemispheres. This promotes a physiological synthesis or integration of the behavioral, emotional, and cognitive levels of the brain. These constitute psychointegration effects—increases in the coherence of brain discharges; an integration of behavior, feelings, and thoughts; and enhanced integration resulting in insight.

The LSD-like psychointegrators interact with serotonergic neurotransmitters across all major levels of the brain, generally augmenting normal processes in activities regulated by serotonergic processes and the structures on which they have effects. Psychointegrators’ effects on neurotransmission reduce habitual repressions, consequently enhancing brain activity and simultaneously stimulating processes that are normally dissociated. Psychointegrators result in the increases in activity of several key areas of the brain:

1. the raphe and reticular formations of the brain stem area that control the amount of information the higher levels of the brain receive;
2. the limbic system, particularly the hippocampus and amygdala, that provides emotional information and personal memories and sense of self; and
3. the visual and auditory areas of the frontal cortex.

SEROTONERGIC AND MACRO-LEVEL EFFECTS OF PSYCHOINTEGRATORS

Serotonin inhibits firing in the raphe area, depressing neuronal firing in lower areas of the brain. LSD-like psychointegrators act on the serotonergic neurons in the locus coeruleus to counteract this inhibition. The locus coeruleus, which serves as a nodal point for convergence of somatosensory and visceral information, has projections which innervate most areas of the neuraxis, principally the thalamus, hypothalamus, cerebellum, basal forebrain, hippocampus, and neocortex. LSD-like psychointegrators also effect serotonin autoreceptors in the raphe,
resulting in a disinhibition of forebrain targets. The release of the tonic inhibitory serotonin effects increases activity in the lateral geniculate nucleus and amygdala, enhancing a key emotional processing center of the brain. LSD-like psychointegrators potentiate serotonin’s excitatory effects on brain stem and spinal cord areas where serotonergic input results in excitatory effects on the cerebral cortex and brain stem.

A basic commonality in the effects of psychointegrators involves disinhibiting the mesolimbic temporal lobe structures. The habitual effect of serotonin in depressing the action of target neurons in the forebrain is blocked by the effects of LSD on serotonin neurons, resulting in the disinhibition of their typical repression, releasing the visual representation processes manifested as visions. The most intense disinhibition and therefore greatest release of activity is on the limbic system’s emotional processing areas and the visual areas of the cortex, resulting in intense visual and emotional experiences. This disinhibition of the mesolimbic temporal lobe structures is manifested in high-voltage synchronous activity in the hippocampus and synchronous discharges in the temporal lobe limbic structures. It results in synchronous theta range (3–6cps) brain wave patterns which drive impulses into the frontal cortex. These discharges replace the typical desynchronized fast wave activity characteristic of the frontal cortex with slower more coherent wave patterns. These coherent discharges produce synchronous slow wave patterns in the frontal lobes, reflecting the discharge patterns of the lower brain structures and causing synchronization of the two sides (hemispheres) of the frontal cortex. These synchronizing effects in the brain are the neurological causes of the integrative experiences of psychointegrators, their potential to produce experience of connection, understanding, and oneness. Psychointegrators stimulate the brain to process information in this integrated fashion.

These combined effects of psychointegrators on the various serotonergic regions of the brain result in the increase in information from the environment, body, and memory; the enhanced experience and recall of emotions, motivations, and cognitive processes; and increases in awareness and internal attention. These diverse effects result in a synthesis of information from the entire brain, enhancing regulation of the autonomic nervous system and integration of emotions and visual–cognitive representations (Winkelman 1996a). Elevation of repressed memories into consciousness permits catharsis and abreaction, allowing conflicts to be integrated and resolved. The tendency of these substances to elicit distressing personal material, unresolved conflicts, repressed experiences, and unintegrated aspects of self suggests that it is their stimulation of the limbic system that provokes the release of distressing material related to the sense of self and social attachments. In addition to their internal effects, the psychointegrators can also increase arousal, heightening sensory receptivity and responsivity to the environment, particularly at low dosages. This, combined with their blockage of some circuitry, contributes to reduced or reversed habituation of typical response patterns, and leads to new patterns of behavior and perspectives.
The limbic-frontal driving elevates information from the behavioral and emotional brains, forcing what is ordinarily unconscious material into the cerebral cortex. This forms the biological process for integrating feelings with thoughts, enhancing integration and insight. Enhanced awareness of repressed memories, combined with increased emotional activation and lability and disruption of habitual behavior patterns, can result in dissolution of egocentric fixations. Psychointegration permits aspects of the self to become reprogrammed into new patterns of thinking and feeling.

**Psychointegrators and the Triune Brain Systems**

Psychointegrators primarily enhance activation of the lower levels of the brain that MacLean (1990, 1993) refers to as the R-complex and the paleomammalian brain, or limbic system. The paleomammalian brain is primarily concerned with self-identity, species survival, family and social relations, as well as learning and memory, and sexual and aggressive emotions and their integration in human behavior. The activation of the paleomammalian brain and its functions by the psychointegrators (and ASCs in general) enhances systemic integration of the psyche. The stimulation of the R-complex by psychointegrators provides an enhanced integration of all areas of the brain; they are responsible for the heightened arousal and awareness, and interference with habituated behavioral routines which the reptilian brain manages. The paleomammalian brain and limbic system provide the social and emotional influences on mentation and behavior.

These primary cognitive processes are based upon nonverbal communication forms of mental and social representation which manage processes and interpretations of emotional and social life. These experiences of lower structures of the brain and consciousness that are elicited by the psychointegrators are discussed by Grof (1975, 1980, 1992) as transbiological realms: the perinatal domain of experiences and the transpersonal domain. The transpersonal domain of the archetypal and mystical structures reveals dimensions of human consciousness and identity beyond (or perhaps better characterized as “below”) egoic identity. Naranjo (1996) suggests that psychedelics activate “Kundalini phenomena” involving levels of organismic self-regulation that emerge as a consequence of the activation of mental structures.

**PSYCHOINTEGRATORS AND CORTICO-STRIATO-THALAMO-CORTICAL FEEDBACK LOOPS**

The effects of the psychointegrators on the brain are complex, reflective of not only the many compounds found in a single plant but also the diverse neurotransmitter system affected in various ways by the plant compounds. For instance, the differences among the psychointegrators include the distinctive empathic qualities of MDMA as opposed to psilocybin. Vollenweider uses advanced imaging and assessment technologies to show that the effects of
Psychedelics differ and derive from the interactions among different neurotransmitter systems and areas of the brain. These involve not just serotonin but also its interactions with the dopamine neurons, GABAergic neurons, and the dopamine–glutamatergic neurotransmitter systems.

The research of Vollenweider (1998) expands this model of the psychointegrative mechanisms of action of psychedelics, emphasizing their selective effects on the brain’s CSTC (cortico-striato-thalamo-cortical) feedback loops. These loops are the principal organizational networks of the brain. These involve parallel and segregated loops that link the information gating systems of lower levels of the brain (specifically the basal ganglia, substantia nigra, and thalamus) with specific regions of the frontal cortex of the brain. These loops are regulated at lower levels of the brain in the thalamus, which limits the ascending information. Vollenweider characterizes the hallucinogens’ effects as involving complex disturbances caused by deficits in the CSTC loops. The psychointegrators disinhibition of these systems floods the frontal cortex with information, leading to breakdown of the integrative capacity of the ego. The limbic loop originates in the hippocampal area and the temporal lobe and projects to ventral striatum, nucleus accumbens, and caudate nucleus, with feedback to the orbitofrontal cortex. These areas exert an inhibitory influence on the thalamus, functioning as “gatekeepers” or filters for the level of the frontal cortex, the basic filtering node for information from the environment and body. Psychointegrators disable this disinhibition process; this increases access to the information capacities. By increasing the flow of information that is ordinarily inhibited, psychedelics permit an overload of information that can overwhelm the frontal cortex.

Vollenweider (1998) reports research that indicates the subcortical loops have an internal functional integrity in their linkages among brain regions and that these are not disrupted by ASCs. ASCs selectively activate different systems. A principal effect of the psychointegrators is on the ego structuring processes. The overload of sensory information produced by the disinhibition overwhelms the cognitive processing capacities and frameworks of the frontal cortex, resulting in fragmentation and dissolution of the inadequate ego structures. This dissolution may be necessary for and contributory to the classic extrovertive mystical experiences of oceanic oneness, connection with the universe made possible by the dissolution of the self-boundary mechanisms.

**Setting Effects and Unique Dynamics as Intrinsic Properties of Psychointegrators**

The effects of psychedelic medicines on psychology include the setting—and these may constitute some of their most important applications in enhancing the context effects, in particular the dynamics of intensive small group interactions. These settings generally develop high degrees of relaxed intimacy, and social cohesion rapidly develops within the groups under the “prosocial” action of DMT. Consequently, psychointegrators can be seen as having adaptive
consequences in terms of reducing, preventing, and interpersonally managing aggressive behavior that can quickly develop in closed, isolated groups (e.g., prisoners, drilling platform workers, remote research groups, and space station teams). Minimizing the inherent dynamic of internal conflict found among humans and other mammalian groups is achieved by ritual processes in the animal world. Among humans these were incorporated into shamanic rituals that used these psychoactive plants as adjuncts to these natural neurochemical processes. A recognized behavioral syndrome caused by chronic, depleted levels of brain serotonin (a tryptamine neurotransmitter) involves poor impulse control, dysphoric-anxious mood, irritability, recklessness, and social ineptitude. These increases in interpersonal discord and aggression are exacerbated by the release of testosterone caused by low levels of brain serotonin, resulting in increased self-detrimental aggression.

The tryptamines methyl analogues such as DMT have an active transport into the brain, enabling it to have the potential to resolve the serotonin depletion syndrome in the fastest way. These substances act much more immediately and effectively in improving serotonin depletion than does the clinical administration of SSRIs (selective-serotonin reuptake inhibitors), which because of autoreceptor self-regulation prevent increased availability of synaptic serotonin during the first two to three weeks of SSRI treatment.5

PSYCHOINTEGRATORS AND THE INTEGRATIVE MODE OF CONSCIOUSNESS

The disinhibition of the serotonergic neurotransmitters systems and the resulting loss of their inhibitory effects upon the mesolimbic temporal lobe structures underlies the common effects of psychointegrators in producing ASC and the widely reported transcendental or transpersonal experience. These systematic changes in brain functioning are common to many means of inducing ASC (Winkelman 1986a, 1992, 2000) or as Mandell (1980, 1985) refers to, the “transcendent states.” This underlying mode of consciousness (Winkelman 2000) is the basis for the universal distribution of shamanistic healing practices (Winkelman 1986b, 1990, 1992).

The overall brain effects of psychedelic medicines are common to diverse means of inducing ASCs, where high-voltage discharges originating in the limbic system replace the normal waking desynchronized fast wave brain patterns with slow wave (theta) cortical synchronization. ASCs in general reflect this pattern of limbic-driven cortical synchronization, reflecting a basic mode of consciousness (Winkelman 2000). The integrative mode of consciousness represents an optimized homeostatic balance among different functional systems of the brain that permits the emergence of integrative or holistic operations of the brain. This integrative mode of consciousness is as fundamental to human psychobiology as the dream, deep sleep, and waking modes of consciousness (see Winkelman 2000).

The psychedelic medicines are the primary exogenous technology humans have to elicit the healing processes produced within the integrating mode of
consciousness. The roles and effects of psychedelic plants in human cultures point to their important psychointegrator functions in meeting human needs by the activation of innate structures that meet basic biological needs; psychedelic medicines enhance the endogenous processes of the brain by augmenting the levels of critical but scarce neurotransmitter effects. Siegal (1990) suggests that humans have an innate drive to alter consciousness, which raises the question of the consequences for a society which views such behavior as aberrant, atavistic, and pathological and criminalizes the very substances which are humanity’s most important technologies for achieving those conditions. The recurrent societal “rediscovery” of ASCs, particularly those associated with current “drug problems,” illustrates the persistent need to seek these states and for societies to adaptively address these issues. Typical cross-cultural patterns of use in regular community ceremonials reflect an adaptation to the episodic psychological needs for their use as psychointegrators. Psychointegrators play a role in managing needs for developmental change or crises-induced problems which require an integration of conscious, preconscious, and unconscious processes, particularly behavioral routines and socioemotional dynamics into a new gestalt or understanding.

CONCLUSIONS

This conjunction of physical medicines—the psychedelics—with the ancient spiritual dynamics of healing reflects neurological concordances, an integration of psychophysiological and psychocultural dynamics. This is reflected in a fundamental adaptation found in all human societies in the form of shamanistic healing practices (Winkelman 1990, 1992, 2000). The particular emphasis upon psychedelics as a means of achieving this adaptation reflects the needs for cultures to reorient their psychocultural dynamics to the changes that have occurred in social and cosmological relations, producing new patterns of integration. This suggests that the use of psychedelics will continue in the rapidly changing world and requires that societies take informed approaches to their managed use. Our contributors take great strides in illustrating the scientific bases for the application of these psychedelic medicines to address crucial health problems, including some of the most vexing problems of our times, those associated with addictions.

NOTES

Thanks to Tom Roberts, Ede Frecska, and John Reisenman for their constructive comments on this chapter.

2. These linking nerve systems have basic functions of motor response and coordination, body coordination with eye movements, emotions, motivations, and executive functions. They manage the body's orientation to external cues, their relationships to internal information (memory and emotion), and their integration into behavior. These cortico-striato-thalamo-cortical linkages are central to the organized coordination of the organism, engaging brain–behavior relationships in coordinating executive decision-making functions with behavioral motivations and social demands. These subcortical pathways have important functions in linking the limbic system with the neocortex and mediating mood and motivations into behavioral responses.

3. The general mechanisms of psychointegrators effects on the brain are described in many sources; I relied primarily on Aghajanian (1984, 1994), Glennon (1990), Jacobs (1984), Jacobs and Gelperin (1981), Kruk and Pycock (1991), Mandell (1980, 1985), McKim (1991), Miller and Gold (1993), Ribeiro (1991), Ryall (1989), and Schmidt and Peroutka (1989). Vollenweider (1998) provides an updated and extended perspective. It is generally accepted that the primary effects of the psychedelic medicines is through their action on the 5-HT$_{1A}$ and 5-HT$_{2}$ serotonergic neurons; there is also binding with the 5-HT$_{3}$ and 5-HT$_{7}$ receptors (Vollenweider 1998).

Serotonin 5-HT$_{1A}$ receptors in the raphe system mediate responses of the serotonergic neurons with respect to their own transmitters; these receptors show a strong sensitivity to LSD-like substances (Aghajanian 1994, p. 140), inhibiting their firing in the raphe area and depressing neuronal firing in lower areas of the brain (the dorsal hippocampus, hypothalamic suprachiasmatic nucleus, amygdaloid cell, caudate-putamen, substantia nigra, trigeminal nucleus, spinal cord interneurons, spinothalamic-tract neurons, and the mesencephalic reticular formation). LSD effects the hippocampus by blocking or suppressing the typical depressant functions of serotonin, permitting the release of responses similar to dreaming, and contributing to production of the typical visual experiences by disinhibiting postsynaptic neurons in the limbic and visual areas.

Indoleamines and phenethylamines cause greater activation of 5-HT$_{2}$ serotonin receptors relative to other serotonin receptors (Aghajanian 1994). Primary effects of LSD-like psychointegrators are through the action on the 5-HT$_{2}$ serotonergic neurons (Glennon 1990, p. 43). Large concentrations of serotonin 5-HT$_{2}$ receptors are in the limbic system in the hypothalamus and basal ganglia; these sensory processing functions are antagonized by LSD (Kruk and Pycock 1991). LSD-like psychointegrators also affect the cerebral cortex and the locus coeruleus 5-HT$_{2}$ receptors (Aghajanian 1994). LSD affinity for 5-HT$_{2A}$ and 5-HT$_{2C}$ receptors facilitates the functioning of the locus coeruleus, which receives numerous somatosensory and visceral inputs and projects diffusely to most of the brain (Miller and Gold 1993).

4. This section is based on personal communication from Ede Frecska.

5. While SSRIs provoke an increase in serotonin in the synaptic cleft as a consequence of presynaptic reuptake blockade in the first two to three weeks of treatment, the brain has multiple feedback mechanism to counterbalance that effect. The normal function of the reuptake pump clears out the synaptic cleft of serotonin and thereby diminishes nerve transmission. The results of blocking this pump are excess synaptic serotonin and postsynaptic receptor stimulation, leading to the accompanying psychomotor activation or agitation that occurs during the initial two to three weeks. The presynaptic autoreceptors provide homeostatic mechanisms, decreasing presynaptic firing when transmitter levels are high in the synaptic cleft. When synaptic serotonin levels are high because of SSRI, presynaptic 5HT receptors decrease the firing of the serotonergic
neuron, and the release of serotonin will decrease. The net sum is that synaptic serotonin will not change significantly for at least two to three weeks. Then as these autoreceptors fatigue, their homeostatic mechanism breaks down, the serotonin level starts to increase, and the antidepressive effect manifests clinically, producing the well-known two to three weeks lag of the antidepressant effect.

REFERENCES


in the United States and Europe (McKenna 2006a). But by and large, these substances remained “hidden”; known only to a few cognoscenti, rarely spoken of or discussed openly, they abided on the margins of society.

All of that changed in the 1960s, and in the decade leading up to it. Albert Hofmann’s profound and (allegedly) accidental discovery of the remarkable properties of the ergot derivative LSD (lysergic acid diethylamide) in 1943 marked a turning point. LSD began to attract the attention of the medical and psychiatric communities in the early 1950s. There was great excitement among psychiatrists and others that the LSD experience could be regarded as a “model psychosis” from which the biochemical mechanisms of mental illnesses could be studied and understood (Grof 1994). Other practitioners saw great therapeutic potential in the new substance. LSD, they asserted, was capable of “dissolving the ego,” and “loosening the boundaries of the self,” and under the right circumstances, these properties could be used to facilitate psychotherapeutic processes. Even the Central Intelligence Agency got into the act, and started to investigate LSD’s potential for brainwashing and mind control (Lee and Shlain 1985). At the same time, neuroscientists became intrigued by its structural similarities to the neurotransmitter serotonin. At the time, the structure of serotonin had been recently characterized, and the discovery that not only was LSD a member of the same chemical family but also had potent effects on serotonin-mediated processes in animals caused great excitement in the neuroscientific community. Some speculated that these discoveries surely pointed to imminent breakthroughs in the scientific understanding of the neurochemistry of consciousness.

Along with this LSD-triggered ferment in the scientific community, similar rumblings were taking place on the cultural front. Aldous Huxley (1954) published his famous book, The Doors of Perception, and this recounting of the author’s experience with mescaline quickly attracted widespread notice and acclaim at least among the intelligentsia and literati. One of the most significant events of the 1950s, in terms of bringing psychedelic drugs to the attention of the masses, had to be the publication of LIFE magazine on May 13th, 1957 (Wasson 1957). That issue chronicled the adventures of amateur ethnomycolo-
gists Gordon and Valentina Wasson in their rediscovery of the shamanic practices involving the use of psilocybin-containing “magic mushrooms” in the mountains of Oaxaca, Mexico. There, in an article enthusiastically headlined “The Discovery of Mushrooms that Cause Strange Visions,” the existence of a centuries-old secret cult of psychedelic mycolatry was thrown right into the face of Middle America. Not that there were any pejorative allusions to the practice at the time; it was reported, National Geographic–style, as simply an interesting adventure by a couple of eccentric travelers. The ancient, and in the eyes of the Spanish Inquisition, blasphemous, practice had been forced underground nearly 400 years previously following savage but ultimately unsuccessful attempts at eradication. Suddenly, there it was in the pages of LIFE magazine for all to see, complete with color photos and beautiful watercolor renderings of the mushrooms in question. Thus did psychedelic drugs make their dramatic debut in the collective consciousness
of America; it may not be much of an exaggeration to state that the “psychedelic sixties” really began with the publication of this article.

At about the same time as Gordon and Valentina Wasson were rambling through the mountains of Oaxaca, in hot pursuit of their momentous rediscovery of the magic mushroom cults of Mexico that brought the psychedelic age into full flower with the publication of their account in *LIFE* magazine in 1957, two icons of the Beat Generation, William Burroughs and Alan Ginsberg, were pursuing a similar but much less noticed quest in the jungles of Ecuador, Colombia, and Peru. Burroughs, Beat poet, famous junkie and homosexual, roustabout, and cultural iconoclast, had long been ahead of his time when it came to the investigation of bizarre drug experiences. In 1953, Burroughs, having gotten wind of an obscure hallucinogen known as *yaje*, set out for South America to find and experience for himself what he was convinced might well be “the final fix.” In a tiny volume, first issued in 1963 by City Lights Books of San Francisco under the title *The Yage Letters*, Burroughs (1963) published an account of his adventures (and misadventures). The book took the form of a series of letters between Burroughs and his friend, fellow poet and countercultural mischief-maker Alan Ginsberg, exchanged as Burroughs wandered from one bizarre scene to another in search of the legendary hallucinogen. Not to be outdone, Ginsberg followed his friend down to South America in 1960 and had his own encounters with the Vine of the Souls; his much shorter account was included in *The Yage Letters* when it was published.2

Burroughs and Ginsberg’s book evolved over nearly a decade. It may truly be said that its publication marked the first irruption of knowledge of this obscure psychedelic decoction into mass consciousness, although it never penetrated very far and remained known only to a few psychedelic cognoscenti until nearly 40 years later. Of course, what was terra incognita to Burroughs and Ginsberg had been known to science since 19th century botanist and explorer Richard Spruce first reported it in 1851 (McKenna 2006b). Following Spruce’s discovery, *ayahuasca* (as the decoction is more commonly known throughout most of the Amazon Basin) became an object of curiosity to pharmacologists and chemists, and a number of investigations ensued that were to stretch over the next 150 years and that continue to the present day (McKenna 2006b).3 It is not entirely clear where Burroughs first learned about *ayahuasca* (or *yaje*, as it is more commonly known in Colombia and Ecuador), but it seems likely he may have stumbled across it in Lewis Lewin’s book, *Phantastica: Narcotic and Stimulating Drugs* (Lewin 1931), during the period of his brief studies at Harvard. It is also possible that while at Harvard, he may have had a chance encounter with legendary ethno-botanist Richard Evans Schultes, the so-called “father of ethnopsychopharmacology,” Spruce’s scientific heir-apparent and for many years the Director of the Harvard Botanical Museum. As stated by *The Yage Letters*, Burroughs and Schultes did not cross paths until 1953 in Mocoa, Colombia; in fact, it seems likely that the most famous picture of Burroughs on his South American travels was taken by Schultes in 1953 (Davis 1996; Harris 2006). If they ever did
meet or discuss yajé at Harvard in the preceding years, there is no record of the encounter.

In any case, by the time Burroughs became interested in ayahuasca/yajé and set out to find it in 1952–53, it was already old news to Schultes. By then, Schultes was coming to the end of more than 12 continuous years of travel and research in South America, and was headed back to his post at Harvard, where he remained as Director of the Botanical Museum until the late 1990s, when encroaching Alzheimer’s disease forced him into retirement (Davis 1996). Following Schultes’ return from the field in the early 1950s, he remained active in the field of ethnopsychopharmacology and eventually evolved into a bit of a countercultural icon himself, as he became more widely known as the world’s expert on hallucinogenic plants. Throughout the 1950s, 1960s, and beyond, Schultes continued his research on ayahuasca and other psychedelic plants, and spawned several generations of eager graduate students who were devoted to their mentor and who continued to investigate the botany, ethnopharmacology, and chemistry of this fascinating Amazonian hallucinogen. To this day, Schultes’ lengthy monograph on the botany and ethnobotany of ayahuasca and its admixture plants, published in the Harvard Museum Botanical Leaflets in 1957 (Schultes 1957), remains a landmark publication on the subject. Subsequent efforts by his graduate students, such as Homer Pinkley and Ara der Marderosian (Der Marderosian et al. 1968; Schultes 1972), built on the foundation of Schultes’ work and further elucidated much of what we now know about the ethnopharmacology of ayahuasca.

Once these shamanic substances had been reintroduced to Western societies, events and cultural dynamics quickly took over. Within a few short years, Timothy Leary emerged on the scene as the self-appointed messiah of psychedelics, especially LSD (even though his initial revelation had come through a chance encounter with mushrooms in Mexico). His slogan, “Turn on, tune in, and drop out,” as slickly crafted as any Madison Avenue ad campaign, quickly became the rallying cry of a new, young, bored generation, disenchanted with the corruption and hypocrisies of postwar institutions and mores, yearning for novel experiences, and more than ready to grab just about any bootstrap that might help lever them up out of the box of conventionality and conformity that had been the defining paradigm of the 1950s (cf. Stevens 1987). Of course, the very same anti-authoritarian slogan that held such appeal for so many young people was equally ominous and frightening to the ossified power structures of the “Establishment,” which was already starting to feel besieged by the sense that things were spiraling out of control as the zeitgeist gathered momentum for its hell-bent gallop toward the unimaginable Millennium, just a few short decades ahead. The Establishment reacted to these accelerating changes, as establishments always have, through brutal repression and persecution, desperate but inevitably doomed attempts to stave off the tsunami of cultural upheaval. Leary and the other advocates of psychedelic substances were denounced, shouted down, and persecuted; the substances themselves, of course, were demonized. As a result, by the end of the
1960s, the hysteria over psychedelics that had swept the country resulted in the ramming through of a number of legislative measures in Congress and local statehouses. Just about any substance that could conceivably be classified as a “psychedelic” (whatever that meant, and even to this day the term is fraught with ambiguity) became prohibited under regulatory schedules that equated them to the most harmful drugs of abuse. The fact that almost nothing was known about their pharmacology, their dangers or possible uses, or even exactly which substances were to be included under the new laws (U.S. Controlled Substances Act of 1970) did not seem to matter. They were classified as “drugs with no medical utility, and a high potential for abuse,” and placed in Schedule I, the most restrictive schedule.

At least, these measures helped “protect” the youth of the nation from this burgeoning threat, or so the legislators and politicians choose to see it. The genie had been put back in the bottle, though of course, not really. What became lost during this period of collective paranoia and ill-considered legislation was the timid, nearly inaudible voice of a few foolhardy souls in the medical and scientific communities who dared to question the wisdom of these actions, who were brave enough to suggest that these substances might have some value or intrinsic interest after all, and who wondered whether, through overreaction, society had lost the opportunity to learn something from them that might ultimately benefit humanity. Of course, given the national mood at the time, these questioners were about as welcome as a drag queen at an American Family Council rally, and so the grumbling of the skeptical few quickly faded from the national dialog. What followed over the next 20 years was the nearly complete suppression of human research with psychedelic substances, although, of course, the substances themselves continued to proliferate throughout society and became ever more widely used. But while “legitimate” clinical research with psychedelics continued at low levels in a few enlightened enclaves in Europe, in the United States the entire field of research became stigmatized and “forbidden.” For a young psychiatrist or neuroscientist of the day to choose psychedelics as his or her primary field of study became about as suicidal a career move as a physicist suddenly opting to study UFO propulsion systems as a primary research specialty.

The blanket prohibition on psychedelic substances that was initiated by the passage of draconian and ill-considered laws at the end of the 1960s served to marginalize and effectively inhibit any clinical investigations with human subjects throughout the 1970s and 1980s. During these decades, the focus of research shifted largely from human studies to animal models and in vitro studies of structure–activity relationships, receptor interactions, and basic research on neurochemistry and neuropharmacology. LSD and many other psychedelic substances evolved into valuable research tools in the hands of neuroscientists, a role which continues to the present day. During this period, this basic research made invaluable contributions to neuroscience, but the disconnection between the findings of basic research and any possible clinical or therapeutic application persisted, primarily due to the discouraging and daunting bureaucratic hurdles that
confronted any legitimate investigator who might wish to expand the scope of their research into the arena of human psychopharmacology. A notable exception to this existed in the person of Dr. Alexander Shulgin, a medicinal chemist and maverick scientist. As a result of several patents arising out of discoveries made during his brief sojourn as a research chemist working for Dow Chemical Company, Shulgin enjoyed a modest income and the freedom to pursue his own independent research while disdaining government funding and all but the most casual institutional affiliations. Working out of his own small lab, “primitive” by any standards, Shulgin synthesized hundreds of psychedelic analogs (which were technically not illegal as they were included on no list of controlled substances) (cf. Shulgin and Shulgin 1991, 1997) and quietly pursued explorations of their psychoactive properties using volunteer test subjects that included Shulgin himself and a small coterie of trip-savvy friends and colleagues. All of this he accomplished with the uneasy permission of various regulatory authorities, who although they frowned on this “forbidden science” could find no means of prohibiting it, since virtually all of the substances investigated were novel compounds not covered under any statutes. Eventually, decades later, the authorities grew tired of Shulgin’s work and concocted an excuse to shut him down, but that is another story (Shulgin and Shulgin 1997). While Shulgin continued to explore the outer fringes of psychedelic psychopharmacology throughout the 1970s and 1980s, he was able to do so because of his unique circumstances. It was not an option available to most young researchers, looking to gain recognition in the competitive world of government-funded Big Science.

That situation only began to turn around, slowly, in 1990, when a young psychiatrist and pineal researcher at the University of New Mexico, Dr. Rick Strassman, decided to tackle the regulatory nightmare head on and filed an Investigational New Drug application with the FDA seeking permission to conduct a small clinical study with DMT (\(N,N\)-dimethyltryptamine), a synthetic alkaloid that was also known to occur naturally in many plants used in shamanic practices in indigenous cultures. DMT was first synthesized by Manske (1931) in the 1930s, but its hallucinogenic properties did not come to light until the 1950s when a researcher at NIMH, Stephen Szara (1956), published the first reports on its bizarre but extremely short-lived effects. At about the same time as Szara’s publications issued, phytochemists were starting to report (sometimes erroneously, cf. Schultes and Raffauf 1960) its occurrence in a number of South American plants used in shamanic practices (Schultes and Hofmann 1980). Several decades later, other researchers reported that not only was DMT widespread in plants but also was a natural constituent of the human brain and pineal gland (Barker et al. 1981). Strassman’s previous work on pineal neurochemistry and particularly the pineal hormone melatonin, also a tryptamine and a close chemical cousin of DMT, led him to apply for permission to investigate its effects in human volunteers. Strassman hypothesized that under some circumstances DMT could be synthesized by the pineal gland and released into the circulation, possibly triggering profound altered states of consciousness such as near-death
experiences. He proposed to investigate this by exploring the psychological and physiological parameters of intravenously administered DMT in a small sample of human subjects with previous experience with hallucinogens. The story of Strassman’s efforts to secure government permission to pursue this research, and its subsequent unanticipated outcome that led him to abandon the field for a number of years, has been marvelously described by the researcher in his compelling book, *DMT: The Spirit Molecule* (Strassman 2001). Although remarkable in itself, Strassman’s research was also a milestone in another respect, in that it forced the door barring clinical investigations on psychedelics slightly ajar. His DMT project did not open a floodgate of new research proposals or trigger a torrent of funding; but his work did have the salutary effect of setting a precedent, and making it somewhat easier for subsequent researchers to obtain permission for clinical studies with psychedelics.

What might be called the modern era of research on *ayahuasca* did not really begin until 1972, when European researchers Rivier and Lindgren (1972) published one of the first interdisciplinary papers on *ayahuasca*, reporting on the alkaloid profiles of *ayahuasca* brews and source plants collected among the Shuar people of the upper Rio Purús in Peru. At the time, their paper was one of the most thorough chemical investigations of the composition of *ayahuasca* brews and source plants that referenced vouched botanical collections. It also discussed numerous admixture plants other than the most commonly employed species, *Psychotria viridis* and *Diplopteris cabrerana*, and for the first time provided evidence indicating that *ayahuasca* admixture technology was complex and that many species were on occasion used as admixtures. In many respects, my own graduate doctoral research on *ayahuasca* (McKenna et al. 1984) was a follow-up to this paper and an attempt to discover answers to some of the unresolved questions raised by the work of Rivier and Lindgren (1972), although my fieldwork was conducted primarily among Mestizo curanderos in Amazonian Peru and not among indigenous groups. Like their work, my investigations included extensive phytochemical analyses of the source plants used in the preparation of *ayahuasca* but had somewhat differing results.

However, this narrative is getting ahead of itself. We must first discuss, for those unfamiliar with the topic, 1) What is *ayahuasca* and what is DMT? and 2) What is the basis of its chemistry and pharmacology? With this as a foundation, we will continue to discuss its potential therapeutic applications.

**WHAT IS AYAHUASCA?**

*Ayahuasca* is a hallucinogenic decoction that is widely used in shamanic practices throughout the Amazon basin. *Ayahuasca* is a Quechua term meaning “vine of the souls,” which is applied both to the beverage itself and to one of the source plants used in its preparation, a large jungle liana (woody vine), *Banisteriopsis caapi* (Spruce ex Griseb.) Morton, in the family Malpighiaceae
While *ayahuasca* is the most widespread term for the beverage, it is also known by other names, including caapi, natema, yaje, and others, in different regions of the Amazon or in different indigenous groups. In Brazil, transliteration of this Quechua word into Portuguese results in the name, *hoasca.* *Ayahuasca* occupies a central position in Amazonian ethnomedicine, and the chemical nature of its active constituents and the manner of its use make its study relevant to contemporary issues in neuropharmacology, neurophysiology, and psychiatry.

In a traditional context, *ayahuasca* is a beverage prepared by boiling—or soaking—the bark and stems of *B. caapi* together with various admixture plants. The admixture employed most commonly is a member of the coffee family (Rubiaceae), *Psychotria viridis* Ruiz & Pavón. The leaves of *P. viridis* contain DMT, an alkaloid that is necessary for the hallucinogenic effect. *Ayahuasca* is unique in that its pharmacological activity is dependent on a synergistic interaction between the active alkaloids in the plant admixtures. The bark of *B. caapi,* one of the components, contains β-carboline alkaloids, which are potent MAO (monoamine oxidase) inhibitors; the other component, the leaves of *P. viridis* or related species, contains the potent short-acting psychoactive agent DMT. DMT is not active when orally ingested, because it is destroyed by MAO in the liver and gut, but it can be rendered orally active if the peripheral MAO is inhibited—and this interaction is the basis of the psychotropic action of *ayahuasca* (McKenna et al. 1984). Other *Psychotria* species reported to be used as admixtures in lieu of *P. viridis* include *P. leiocarpa, P. nervosa, P. carthaginensis,* and *P. poeppigiana.* There is little chemical data to confirm the presence of DMT in these other species, but the fact that they are employed provides at least anecdotal evidence that they also contain the active principle.

In the Northwest Amazon, particularly in the Colombian Putumayo and Ecuador, the leaves of *Diplopterys cabrerana* (Cuatr.) Gates are added to the brew instead of the leaves of *P. viridis.* This woody vine is in the same family as *Banisteriopsis* and morphologically resembles it. The chief alkaloid present in *Diplopterys,* however, is DMT, the same compound as in the *Psychotria* admixtures, and pharmacologically, the effects are similar. In Peru, various admixtures in addition to *Psychotria* or *Diplopterys* are frequently added, depending on the magical, medical, or religious purposes for which the drug is being consumed. Although a virtual pharmacopoeia of admixtures (McKenna et al. 1995) is occasionally added, the most commonly employed admixtures (other than *Psychotria,* which is a constant component of the preparation) are various members of the nightshade family (Solanaceae), including tobacco (*Nicotiana* sp.), *Brugmansia* sp., and *Brunfelsia* sp. (Schultes 1972; McKenna et al. 1995). These solanaceous genera are known to contain alkaloids, such as nicotine, scopalamine, and atropine, which effect both central and peripheral adrenergic and cholinergic neurotransmission. “Nightshade” alkaloids (tropanes) such as scopalamine, and *ayahuasca* preparations containing nightshades, can be more dangerous than psychedelics, such as DMT, or brews lacking these
additives, as nightshades can cause a profound state of disorientation and delirium, often accompanied by amnesia. In practice, however, these additives are rarely added to the ayahuasca preparation, and often, when they are added, only a “symbolic” small amount is added, insufficient to produce a full pharmacological effect.

**ACTIVE CONSTITUENTS OF AYAHUASCA AND ITS SOURCE PLANTS**

The chemical constituents of ayahuasca and the source plants used in its preparation have been well characterized (Rivier and Lindgren 1972; McKenna et al. 1984; Callaway et al. 2005). *B. caapi* contains the β-carboline derivatives harmine, THH (tetrahydroharmine), and harmaline as the major alkaloids. The admixture plant, *Psychotria viridis*, contains a single major alkaloid, DMT (Rivier and Lindgren 1972; McKenna et al. 1984). The concentrations of alkaloids in the ayahuasca beverages are, not surprisingly, several times greater than in the source plants from which they are prepared, based on a quantitative analysis of the major alkaloids in several samples of ayahuasca collected on the upper Rio Purús. McKenna et al. (1984) reported somewhat higher values for the alkaloid content of several samples of Peruvian ayahuasca, well within the range of activity for DMT administered i.m. (Szara 1956) or i.v. (Strassman and Qualls 1994) and also for harmine to act effectively as a MAOI (monoamine oxidase inhibitor). A recent study by Callaway et al. (2005) examined the variations in alkaloid profiles of DMT, harmine, harmaline, and THH in 29 ayahuasca decoctions obtained from the UDV (União do Vegetal) church, the Santo Daime church, the Shuar tribe, and the Barquinha church. There are obviously considerable variations in alkaloid content of ayahuasca decoctions, and this is readily explained by differences in the methods of preparation, as well as in the natural variations to be expected in the source plants. This conclusion is now well supported and documented in the recent papers by Callaway et al. (2005) and Callaway (2005).

**PHARMACOLOGICAL ACTIONS OF AYAHUASCA AND ITS ACTIVE ALKALOIDS**

The oral activity of ayahuasca is a function of the peripheral inactivation of MAO by the β-carboline alkaloids in the mixture. This action prevents the peripheral oxidative degradation of the DMT, which is the primary hallucinogenic component, rendering it orally active and enabling it to penetrate the blood/brain barrier and reach its site of action in the central nervous system in an intact form (Schultes 1972; McKenna et al. 1984). DMT alone is inactive following oral administration at doses up to 1,000mg (Shulgin 1982; Nichols et al. 1991).
DMT is active by itself following parenteral administration (a route of administration other than oral ingestion, e.g., by smoking the free base or by injection) at around 25 mg (Szara 1956; Strassman and Qualls 1994). Because of its oral inactivity, users employ various methods of parenteral administration. For example, drug abusers using synthetic DMT commonly smoke the free base; in this form, the alkaloid volatilizes readily and produces an immediate, intense psychedelic episode of short duration (5–15 min), usually characterized by multicolored, rapidly moving hypnagogic hallucinations (Stafford 1977). The Yanomamo Indians and other Amazonian tribes prepare a snuff from the sap of various species in the genus Virola that contains large amounts of DMT and the related compound, 5-methoxy-DMT, which is also orally inactive (Schultes and Hofmann 1980; McKenna et al. 1985). The effects of the botanical snuffs containing DMT, while not as intense as smoking DMT freebase, are similarly rapid in onset and of limited duration. The ayahuasca beverage is unique in that it is the only traditionally used psychedelic where the peripheral inactivation of DMT present in one plant is prevented by combining it with another plant containing potent and selective MAO-A inhibitors. The psychedelic experience that follows ingestion of ayahuasca differs markedly from the effects of parenterally ingested DMT; the time of onset is approximately one hour after ingestion, and the effects last approximately four hours. Usually the subjective effects are less intense than those of parenterally administered synthetic DMT. The subjective effects of ayahuasca include hypnagogic hallucinations, dream-like reveries, and a feeling of alertness and stimulation. Peripheral autonomic changes in blood pressure, heart rate, etc. are also less pronounced in ayahuasca than parenteral DMT. In some individuals, transient nausea and episodes of vomiting occur, while others are rarely affected in this respect. When ayahuasca is taken in a group setting, vomiting is considered a normal part of the experience and allowances are made to accommodate this behavior (Callaway et al. 1999).

The amounts of β-carbolines present in a typical dose of ayahuasca are well above the threshold for activity as MAOI. It is likely that the main contribution of the β-carbolines to the acute effects of ayahuasca results from their oral activation of DMT, through their action as peripheral MAOI. It is worthy of note that β-carbolines are highly selective inhibitors of MAO-A, the form of the enzyme for which serotonin and presumably other tryptamines, including DMT, are the preferred substrates (Yasuhara et al. 1972; Yasuhara 1974). This selectivity of β-carbolines for MAO-A over MAO-B, combined with their relatively low affinity for liver MAO compared to brain MAO, may explain why reports of hypertensive crises following the ingestion of ayahuasca are rare or nonexistent.

β-Carboline, by themselves, may have some psychoactivity and thus may contribute to the overall psychotropic activity of the ayahuasca beverage; however, it is probably inaccurate to characterize the psychotropic properties of β-carbolines as “hallucinogenic” or “psychedelic” (Shulgin and Shulgin 1997). As MAO inhibitors, β-carbolines can increase brain levels of serotonin, and the primarily sedative effects of high doses of β-carbolines are thought to result from
their blockade of serotonin deamination. The primary action of β-carbolines in the ayahuasca beverage is their inhibition of peripheral MAO, which protects the DMT in the brew from peripheral degradation and thus renders it orally active. There is evidence, however, that THH, the second most abundant β-carboline in the beverage, acts as a weak 5-HT uptake inhibitor and MAOI (Buckholtz and Boggan 1976, 1977). Thus, THH may prolong the half-life of DMT by blocking its intraneuronal uptake, and consequently, its inactivation by MAO. On the other hand, THH may also block serotonin uptake into the neuron, resulting in higher levels of 5-HT in the synaptic cleft; this 5-HT, in turn, may attenuate the subjective effects of orally ingested DMT by competing with it at postsynaptic receptor sites (Callaway et al. 1999).

DMT and its derivatives and the β-carboline derivatives are widespread in the plant kingdom (Smith 1977; Allen and Holmstedt 1980), and both classes of alkaloids have been detected as endogenous metabolites in mammals, including humans (Airaksinen and Kari 1981; Barker et al. 1981; Bloom et al. 1982). Methyl transferases which catalyze the synthesis of DMT, 5-methoxy-DMT, and bufotenine have been found to occur naturally in human lung, brain, blood, cerebrospinal fluid, liver, and heart, and also in rabbit lung, toad, mouse, steer, guinea pig, and baboon brains, as well as in other tissues in these species (McKenna and Towers 1985). Although the occurrence, synthesis, and degradative metabolism of DMT in mammalian systems have been the focus of scientific investigations (Barker et al. 1980, 1981), the possible neuroregulatory functions of this psychotomimetic compound are incompletely understood. Endogenous psychotogens have been suggested as possible etiological factors in schizophrenia and other mental disorders, but the evidence remains equivocal (Fischman 1983).

β-Carbolines are tricyclic indole alkaloids that are closely related to tryptamines, both biosynthetically and pharmacologically. They are readily synthesized via the condensation of indoleamines with aldehydes or alpha-keto acids, and their biosynthesis probably also proceeds via similar reactions (Melchior and Collins 1982). 6-Methoxy-tetrahydro-β-carboline has been identified as a major constituent of human pineal gland (Langer et al. 1984). This compound inhibits the high-affinity binding of [3H]-citalopram to 5-HT transporters in rat brain (Pahkla et al. 1997), and also significantly inhibits 5-HT binding to type 1 receptors in rat brain; the compound has a low affinity to type 2 receptors, however (Taylor et al. 1984). There are implications for this action of tetrahydro-β-carbolines for the pharmacology of ayahuasca. Inhibition of 5-HT uptake by THH, present in significant amounts in ayahuasca, may elevate the concentrations of 5-HT at receptor sites, thus attenuating the hallucinogenic effects of DMT by competitive inhibition at the receptor sites. Additionally, elevated synaptic levels of DMT and 5-HT, both 5-HT agonists, could potentially trigger “serotonin syndrome” if also combined with SSRI (selective serotonin reuptake inhibitors)-type antidepressants. 2-Methyl-tetrahydro-β-carboline and harman have been detected in human urine following ethanol loading (Rommelspacher et al. 1980). It has been suggested that endogenous β-carbolines and other...
As research on psychedelic medicine advances, further refinements in screening, safety and therapeutic protocols will be possible. Questions for future research. Numerous scientific and empirical questions remain in the field of psychedelic medicine. The re-emerging paradigm of psychedelic medicine may open clinical and therapeutic doors long closed. Key points. Medical interest in psychedelic drugs as treatments for illnesses such as anxiety, addiction and posttraumatic stress disorder has been renewed. Therapeutic effects of ritual ayahuasca use in the treatment of substance dependence qualitative results. J Psychoactive Drugs 2014:46:63-72. OpenUrl CrossRef PubMed.