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Altered States of Consciousness
Drug-Induced States

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Drugs are chemicals that in small amounts have significant impact on body function. Drugs have their origins in plant and fungal medicines – and many drugs come directly from plants or fungi, are derived from chemicals that come from plants or fungi, or are synthetic compounds inspired by substances originally identified in plants or fungi. There is a long history of relationships between people and psychoactive plants and fungi, with far-reaching impact on human societies – witness coffee, tea, chocolate, tobacco, alcoholic beverages, cannabis, opium, and a multitude of herbs and spices.

William James was a pioneer in the study of mind within the context of modern science. In his classic 1890 text *The Principles of Psychology* he drew attention to the powerful influences drugs can have on the psyche, writing of the consciousness-altering effects of "a very few ounces of alcohol or grains of opium or hasheesh, or a whiff of chloroform or nitrous oxide gas" (James 1890, p. 4). Particularly impressive to him were the effects of nitrous oxide, a substance first synthesized by Joseph Priestley in the 1770s and later studied by Humphry Davy. In 1800, the 21-year-old Davy published a massive book describing his experiments with nitrous oxide, the first investigation in the era of modern chemistry of a specific chemical substance's impact on consciousness. Introduced into medicine and dentistry as an anesthetic gas in the mid-1800s, nitrous oxide came to James' attention in the 1870s and he wrote about his personal experience in an essay published in the philosophy journal *Mind*: "the keynote of the experience is the tremendously exciting sense of an intense metaphysical illumination. Truth lies open to the view in depth beneath depth of almost blinding evidence. The mind sees all the logical relations of being with an apparent subtlety and instantaneity to which its normal consciousness offers no parallel …" (James 1882, p. 206).

Twenty years on, when James delivered the Gifford Lectures at the University of Edinburgh, his experiences with nitrous oxide remained of great importance. His comments on this are among the most eloquent passages ever written about altered consciousness:

> One conclusion was forced upon my mind at that time, and my impression of its truth has ever since remained unshaken. It is that our normal waking consciousness, rational consciousness as we call it, is but one special type of consciousness, while all about it, parted from it by the filmiest of screens, there lie potential forms of consciousness entirely different. We may go through life without suspecting their existence; but apply the requisite stimulus, and at a touch they

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> are there in all their completeness, definite types of mentality which probably somewhere have their application and adaptation. No account of the universe in its totality can be final which leaves these other forms of consciousness quite disregarded. How to regard them is the question, – for they are so discontinuous with ordinary consciousness. Yet they may determine attitudes though they cannot furnish formulas, and open a region though they fail to give a map. At any rate, they forbid a premature closing of our accounts with reality.
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> *(James 1902, p. 388)*

William James appreciated that to better understand the mind and its relation to the body, any and all phenomena of relevance to these questions ought be investigated. How could one hope to understand the nature of consciousness without taking seriously such profound drug-induced altered states of awareness?

The effects of drugs on consciousness are currently understood to occur via their interactions with cellular and molecular processes within the nervous system. Whether or not this is the whole story remains to be seen.

Neurons and Synapses

The human brain contains roughly 100 billion (10^{11}) nerve cells (neurons) of various types, and at least that number of glial cells (glia) of various sorts. Signals move between cells at connections called synapses, which are of two major types – electrical and chemical. Electrical synapses consist of channel proteins through which ions may directly pass from one cell to another, permitting certain kinds of signal information to rapidly propagate between cells. Chemical synapses are narrow (~20 nanometers) gaps or clefts between cells at which neurotransmitter molecules carry signal information from one cell to another. There are hundreds of trillions of synaptic connections within the human brain. This alone makes for staggering complexity.

The signaling scenario at a chemical synapse goes something like this. A nerve impulse propagates along a neuronal axon as a sort of wave of electric current. When the impulse reaches the presynaptic axon terminal, storage vesicles containing neurotransmitter molecules are induced to fuse with the boundary membrane of the axon and release neurotransmitter molecules into the synaptic cleft. Neurotransmitter molecules rapidly diffuse throughout the synaptic cleft and interact with receptor proteins on the postsynaptic neuron, the presynaptic axon terminal, and other nearby neurons and glia.

A receptor protein may be of the ionotropic type, where interaction of neurotransmitter with receptor shifts the shape of the receptor, opening a channel within the protein that allows particular types of ions to flow across the cell membrane. The result is a rapid effect on membrane voltage, either increasing or decreasing the excitability of the cell receiving the signal.

Or, the receptor may be of the metabotropic or GPCR (G-protein coupled receptor) type. When a neurotransmitter molecule binds to a GPCR, the resulting shift in shape of the receptor protein facilitates the binding of an intracellular G-protein to the GPCR. The G-protein then becomes "activated" and goes on to have a variety of possible effects, among which are impact on cell excitability via actions on ion channels, changes in cell metabolism through actions on enzymes, and changes in gene transcription through actions on transcription-factor proteins. GPCRs and their intracellular couplings are systems of profound versatility!

In order to prepare the synapse for the next signal, neurotransmitter molecules must be removed from the synaptic cleft so that new signals may be differentiated from prior ones. Located in the membrane of the presynaptic axon terminal are uptake transporter proteins that move specific neurotransmitters from the synaptic cleft back into the interior of the axon terminal. In some cases, enzymes are present that rapidly inactivate neurotransmitter molecules by catalyzing specific chemical alterations.

Among the postsynaptic actions of some neurotransmitters is a triggering of the synthesis of molecules that diffuse back across the synaptic cleft and have effects at the presynaptic axon terminal, either by binding to receptors or by interacting in other ways with cellular chemistry. These retrograde (backward moving) signals are involved in the regulation of signal activity at synapses, via feedback effects that can alter the strength of the synapse.

Chemical synapses thus have a stunning capacity to finely regulate the signaling activity between cells. And GPCR receptors can have long-term effects on synaptic activity via influences on gene transcription. For example, synthesis of growth-factor proteins can be modulated, with impact on neurogenesis, growth and branching of dendrites and axons, and formation of dendritic spines. Thus, new synapses can be formed, and existing synapses can become more elaborate and strong, or become weaker and even deconstruct. Expression of genes for metabolic enzymes can have an impact on the quantity of neurotransmitter synthesized and loaded into storage vesicles, as well as how rapidly neurotransmitter is degraded. Regulation of gene expression for neurotransmitter receptors, uptake transporters, and the components of the various steps involved in intracellular G-protein coupling pathways allows for nuanced tuning of the strengths of synapses. These processes of changing the patterns and strengths of synapses in the brain are collectively referred to as "neuroplasticity." Such processes are intimately involved in learning and memory, to the extent that memory is hypothesized to reside in the activity of networks of neuronal connectivity.

The most abundant neurotransmitter in the human brain is glutamic acid (or glutamate), a molecule that has excitatory signaling effects when acting at ionotropic glutamate receptors. The second most abundant neurotransmitter in the human brain is gamma-amino butyric acid (GABA), a molecule that has inhibitory effects when acting at ionotropic $GABA_A$ receptors. Each of these neurotransmitters is released by billions of neurons and has effects at trillions of synapses.

Other neurotransmitters in the human brain include the monoamines: serotonin (5HT or 5-hydroxytryptamine), norepinephrine, dopamine, and histamine. Each of these neurotransmitters is produced by clusters of cells in the brainstem: serotonin in the raphe nuclei, norepinephrine in the locus coeruleus, dopamine in the substantia nigra and ventral tegmentum, and histamine in the tuberomammillary nucleus of the hypothalamus. In each case, the number of cells producing and releasing these neurotransmitters is relatively small, on the order of a hundred thousand or so. However, because these cells send axons throughout large parts of the cerebral cortex and other parts of the brain, these neurotransmitters have impact on billions of neurons.

Several dozen additional molecules are presently known to function as neurotransmitters in the human brain. Among them are glycine, adenosine, adenosine triphosphate (ATP), nitric oxide, endocannabinoids such as anandamide and 2-arachidonylglycerol (2AG), oxytocin, vasopressin, substance P, orexins, and more than a dozen different opioid peptides or endorphins. Dimethyltryptamine (DMT), tryptamine, octopamine,

and other so-called trace amines may also function as neurotransmitters (Premont, Gainetdinov, & Caron 2001; Jacob & Presti 2005).

The dominant receptors for glutamate and GABA are of the ionotropic type, allowing glutamate and GABA to have rapid excitatory and inhibitory effects on neuronal activity. Acetylcholine (acting at nicotinic acetylcholine receptors), serotonin (acting at $5HT_3$ receptors), ATP acting at purine-2X receptors, and glycine are the other neurotransmitters presently known to have ionotropic receptors. In addition to their ionotropic effects, glutamate, GABA, and ATP also act at GPCRs. Muscarinic acetylcholine receptors and all the serotonin receptors other than $5HT_3$ are GPCRs. All other known neurotransmitter receptors – dopamine, norepinephrine, histamine, adenosine, opioid, cannabinoid, and so forth – are GPCRs. Thus, the effects of many neurotransmitters, as well as drugs that act via these neurotransmitter receptors, can have rapid effects on neuronal excitability, as well as longer-term modulatory effects on excitability, metabolism, gene transcription, and synaptic connectivity.

Drugs and Brain Neurobiology

The effects of psychoactive drugs on the brain – and thus, it is believed, on consciousness – are at the present time almost exclusively described in terms of the chemical interactions between the drugs and the various molecular components of nerve cells, with the primary sites of interaction understood as being at chemical synapses. For example, some drugs are known to be agonists at neurotransmitter receptors, binding to and activating a receptor in a manner similar to that of the endogenous neurotransmitter. Some drugs are antagonists at receptors, binding to the receptor and blocking the action of neurotransmitters or other agonists. Some drugs bind to receptors and enhance or otherwise modulate the action of endogenous neurotransmitters. Some drugs interact with uptake transporters, blocking them or causing them to malfunction in other ways. And some drugs impact the synthesis or degradation of specific neurotransmitters.

The most widely used psychoactive drug in the world is caffeine, usually ingested by way of the plants tea (*Camellia sinensis*), coffee (*Coffea arabica*), and cacao (*Theobroma cacao*, source of chocolate). Other caffeine-containing plants include guarana, kola, yaupon, and yerba mate. And these days, a great deal of caffeine is consumed via caffeinated and sugared soft-drink and energy-drink products. Caffeine acts as an antagonist at receptors for adenosine, an inhibitory neurotransmitter in the brain. By antagonizing adenosine receptors and blocking adenosine's inhibitory effects, caffeine produces excitation in the nervous system. This is believed to be the basis for caffeine's experiential effects – increased wakefulness and alertness. Related molecules such as theophylline, found in tea, and theobromine, found in cacao, act in a similar fashion.

Other drugs that are nervous-system stimulants include cocaine, from the coca plant (*Erythroxylum coca*), ephedrine from the *Ephedra* plant, cathinone from the khat plant (*Catha edulis*), and the synthetic pharmaceutical amphetamine, a chemical cousin of ephedrine and cathinone. Pharmaceutical-chemical relatives of amphetamine include methamphetamine and methylphenidate. All these drugs act primarily at uptake transporters for dopamine and norepinephrine, blocking uptake of released neurotransmitter (in the case of cocaine) and causing leakage of neurotransmitter out of the axon terminal via the uptake transporter (in the case of amphetamine and related chemicals).

In all cases, there is enhanced activity at synapses using dopamine and norepinephrine and a resulting arousal of cortical activity.

Alcohol (here referring to ethyl alcohol or ethanol) is a drug that has an opposite effect on consciousness to that of the stimulants described above. Decreased arousal and increased relaxation are the hallmarks of low doses of alcohol and other sedative-hypnotic drugs, a category that also includes barbiturates (such as the pharmaceuticals phenobarbital, secobarbital, thiopental, etc.), benzodiazepines (diazepam, lorazepam, alprazolam, etc.), and general anesthetics (diethyl ether, halothane, sevoflurane, propofol, etc.). All these sedative-hypnotics produce, in a dose-dependent manner, decreased arousal, amnestic effects ("blacking out"), loss of waking consciousness, and death from shutdown of parts of the brain controlling vital functions of the body. Sedative-hypnotic drugs all appear to have a common mechanism of action – binding to one of several locations on ionotropic $GABA_A$ receptors and enhancing the inhibitory action of GABA when it binds to the receptor. This correlates behaviorally with decreased arousal, sedation, and loss of waking consciousness (Franks 2008).

Tobacco (*Nicotiana tabacum*), with its identified primary psychoactive constituent, nicotine, is one of the most widely used psychoactive substances in the world. Tobacco is also among the most powerful of plants, with effects on consciousness that are at once subtle and profound – mentally stimulating and focusing, anxiolytic and grounding. Nicotine acts as an agonist at nicotinic acetylcholine receptors found throughout the brain. These are ionotropic positive-ion channels that have excitatory effects on neurons.

The seed from the Southeast Asian palm tree *Areca catechu* also ranks among the most widely used psychoactive substances in the world. The areca nut is frequently referred to as betel nut, because it is often consumed together with leaves from *Piper betel*, a plant cousin to black pepper (*Piper nigrum*). Not widely known in Europe and the Americas, the areca nut is used by millions of people daily in India, Taiwan, Thailand, and other regions of south Asia. Like all plant substances, it contains numerous molecular constituents, a number of which are likely to have physiological activity. Arecoline has been identified as a primary psychoactive component of areca nut, and its major known neurochemical action is agonism at muscarinic acetylcholine receptors. The effects are a combination of mental alertness and body relaxation.

Opioids are molecules that act on the body like opium from the opium poppy, *Papaver somniferum*. Morphine and codeine are the primary psychoactive constituents of opium. Effects of opioids include profound analgesia (reduced perception of pain), cough suppression, sedation, and hallucinatory dreaminess. Slowing of respiration can result in death if the dose is sufficiently large. Opioid receptors are GPCRs that have been classified into several subtypes (mu, delta, kappa) based on their pharmacology, protein structure, and distribution in the brain.

Preparations from the *Cannabis* plant, such as marijuana and hashish, have been consumed for their medicinal and consciousness-altering effects for millennia. Cannabis contains a large variety of molecules called cannabinoids, found nowhere else in the plant world. The most psychoactive of these constituents has been identified as delta-9-tetrahydrocannabinol, or THC, and the interaction of THC with the nervous system is via agonist actions at the cannabinoid receptor, CB_1. This receptor, discovered in 1989, is the most abundant GPCR in the mammalian brain and is often located on presynaptic axon terminals. Endogenous neurotransmitter ligands, the endocannabinoids, are generated in postsynaptic dendrites and carry signals from the postsynaptic cell to the

presynaptic cell – retrograde signaling believed to be an important factor in adjusting synaptic strength.

Thus, a large variety of plants and chemicals have long been appreciated for the effects they have on consciousness. In many instances these alterations of consciousness may reduce anxiety, at least over the short term. This can contribute to a desire to repeat the experience. With repetition the neural circuitry associated with intoxication is strengthened, making the behaviors leading to that state more robust and reinforced. If the drive toward intoxication develops into compulsive behavior having adverse effects on one's ability to function, it is termed addiction. Many drugs having the potential to produce addiction have been found to directly or indirectly increase activity in neural pathways connecting the ventral tegmentum to the nucleus accumbens and the frontal cortex. The primary neurotransmitter in these so-called reward pathways is dopamine.

Thus far all discussion has concerned drug effects on proteins associated with cell membranes at chemical synapses. This is often the only thing considered relevant for the effects of drugs on consciousness, and the only thing discussed, even in massive textbooks on psychopharmacology. However, cells have far more going on than just surface membrane proteins. Drugs that enter the brain cross the blood-brain barrier by virtue of being sufficiently lipid soluble to diffuse through the phospholipid bilayer membranes forming the boundaries of the cells making up the walls of the blood vessels. Similarly, for the same reason, any such drug will also be diffusing across the boundary membranes of neurons and glia and entering the interiors of these cells. Inside cells there are large numbers of structures that drug molecules may interact with, having who knows what effects. Our capacity to conduct pharmacological studies at this level is both limited by technology and by lack of a community of interest.

One hypothesized novel pharmacologic mechanism posits that the consciousness-obliterating effects of general anesthetics result from binding to intracellular microtubules (Hameroff 2006; Craddock et al. 2012), protein polymers forming part of the internal scaffolding within cells – the cytoskeleton. The cytoskeleton is involved in movement of neurotransmitter vesicles, trafficking membrane proteins (such as receptors) to cell surfaces, and dynamic neuroplastic growth and branching of axons and dendrites. Such things introduce multiple possible mechanisms by which intracellular binding of drugs to microtubules, as well as other structures in the interiors of cells, might contribute to their pharmacologic actions. Certainly, we remain far from understanding the behavioral effects of most drugs – from general anesthetics to stimulants to psychedelics – based on what is currently known about their membrane-receptor neurochemistry.

Psychedelics and Consciousness

The most interesting of the chemicals known to impact consciousness are the psychedelics. The various terms used to describe this class of substances – psychedelic (mind revealing), hallucinogen (generating hallucinations), psychotomimetic (mimicking psychosis), entheogen (generating god within) – speaks to the complexity of their effects. Feelings, thoughts, and perceptions become intensified and available to awareness in ways not ordinarily experienced. Among all known psychoactive drugs, the psychedelics are most influenced by what is called set and setting: intention, expectation, preparation, physical and social setting, and other aspects of context may have

profound effects on the nature of the altered-state experience and the resulting short- and long-term impact. These altered states of consciousness may be characterized by a diminution of Freudian psychological defenses, allowing material not ordinarily available to awareness to become more accessible. It is this property that contributes to the psychotherapeutic utility of the psychedelics (Grof 2001).

Many psychedelic plants and fungi have long histories of use by indigenous cultures. In such cultures, the medicine people, healers, or shamans may employ psychedelic plants or fungi to catalyze healing or divination. Among such agents are *Psilocybe* mushrooms, containing the psychoactive chemical components psilocin and psilocybin; *Virola* (Epeña) and *Anadenanthera* (Yopo) snuffs from the Amazon, containing dimethyltryptamine (DMT); *Psychotria* and other DMT-containing plants from the Amazon, mixed together with the *Banisteriopsis caapi* ayahuasca vine to make ayahuasca brew or yagé; *Tabernanthe iboga* from west-central Africa, containing ibogaine; and peyote, San Pedro, and other cacti from the Americas, containing mescaline (Schultes and Hofmann 1980).

One of the most famous psychedelic chemicals is LSD, lysergic acid diethylamide, first made by Albert Hofmann in 1938 as one of a series of chemical derivatives of ergotamine isolated from *Claviceps* fungus. He made it again in 1943 and at that time discovered its potent psychoactive effects. Hofmann quickly appreciated that he had discovered something very profound (Hofmann 1980). In the 1940s the brain was not described as a neurochemical system in the way it is today. That a tiny amount of chemical could have such a stunning impact on consciousness was a pivotal event in the early development of biological psychiatry and of molecular neuroscience. The similarity of molecular structure between serotonin and a portion of the LSD molecule led to early speculations on brain chemistry and mental illness (Woolley and Shaw 1954; Nichols and Nichols 2008). Around the same time, the structural similarity of mescaline to epinephrine and norepinephrine also prompted speculations about relationships between body chemistry and mental illness (Osmond & Smythies 1952).

LSD, DMT, psilocin (and its pro-drug psilocybin), and mescaline are often referred to as "classical psychedelics," and all have substantial agonist activity at type-2A serotonin ($5HT_{2A}$) receptors (Nichols 2004; Nichols 2016). Some of the newer synthetic psychedelic substances – such as DOI (2,5-dimethoxy-4-iodoamphetamine) and DOB (2,5-dimethoxy-4-bromoamphetamine) (Shulgin & Shulgin 1991) – also have psychoactive effects similar to classical psychedelics and are known to have substantial $5HT_{2A}$ agonist activity. This has led to a hypothesis that the $5HT_{2A}$ receptor may be the primary mediator of the unique effects of psychedelic drugs.

$5HT_{2A}$ GPCR serotonin receptors are widely distributed throughout the brain, especially in the cerebral cortex (Nichols & Nichols 2008). Other serotonin receptor subtypes (especially $5HT_{2C}$ and $5HT_{1A}$), dopamine receptors, and trace amine receptors, as well as other neurotransmitter receptors, may also play significant roles in the actions of psychedelics.

While the consciousness-altering effects of various classical psychedelics have much in common, there are also differences in the effects of different drugs. Eventually it may be possible to connect the subjective signatures of different psychedelic drugs to their differing neurochemical actions in the brain. For example, serotonin and other agonists at the $5HT_{2A}$ receptor activate multiple GPCR-mediated intracellular signaling pathways, and the relative activation of pathways varies among different agonists at the $5HT_{2A}$ receptor (Nichols 2004; Nichols 2016).

One particularly profound effect of the classical psychedelics is their ability to facilitate the formation of powerful memories of circumstances experienced during periods of intoxication. Experiences of insight and transcendence may have lifelong positive benefits, and experiences of anxiety or panic may have long-term negative impact. This suggests that the classical psychedelics have a powerful impact on neuroplasticity. Perhaps this phenomenon might eventually be understood in terms of agonist actions at $5HT_{2A}$ receptors and subsequent impact on cortical excitability as well as local synaptic plasticity (Béïque et al. 2007). And perhaps there is more to the picture, much more.

There are a number of substances that may be called psychedelic, but are not "classical psychedelics." Among these are methylenedioxymethamphetamine (MDMA), *Salvia divinorum* and salvinorin A, the *Amanita muscaria* mushroom, tropane alkaloids and the plants from which they come, *Cannabis* and delta-9-tetrahydrocannabinol, ketamine, nitrous oxide, and carbogen. Although these substances also have "mind-manifesting" characteristics, the experiences they produce are qualitatively different from those of the classical psychedelics, and their known interactions with the nervous system also differ from $5HT_{2A}$ receptor agonism.

Methylenedioxymethamphetamine (MDMA), popularly known by the street name "ecstasy," has psychedelic intensification of thoughts and feelings. In addition, there are enhanced feelings of connection with others, reduced anxiety, and a greater ability to verbalize feelings. This makes MDMA a powerfully effective facilitator of psychotherapeutic process, and it has proven to be especially valuable in the treatment of post-traumatic stress disorder (PTSD) (Mithoefer et al. 2013). Chemically related to methamphetamine, MDMA also produces central and sympathetic nervous system stimulation, as well as euphoria. While MDMA has been found to interact with several transporters and receptors in the brain, its primary identified effect is to facilitate release of serotonin from axon terminals via leakage through uptake transporters.

Salvia divinorum, a plant from the mint family having a history of shamanic use among the Mazatecs of southern Mexico, produces profound alterations of consciousness when ingested. Although hallucinogenic in nature, the character of the altered state is very different from that produced by classical psychedelics, and is described as a uniquely powerful and yet subtle portal into the psyche (Pendell 2010a). The primary psychoactive chemical component was identified in the early 1980s as salvinorin A, a non-alkaloid molecule subsequently found to be a highly selective agonist at the kappa-opioid receptor (Valdés 1994; Roth et al. 2002). Very little is known about the functions of kappa-opioid receptors in the brain. Among the endogenous ligands are dynorphin peptides, members of the opioid peptide (endorphin) family.

Amanita muscaria is a mushroom found throughout the world and recognized by its distinctive red cap with whitish "warts." In part because of its striking appearance it is perhaps the world's most famous mushroom. Although its psychoactive effects have been described as hypnotic and even deliriant-like, it also has a folkloric and shamanic history of use, and some have described its effects as remarkable (Pendell 2010b). R. Gordon Wasson suggested that *Amanita muscaria* was the basis for the legendary Soma, a ritual drink praised in the 3,000-year-old collection of Sanskrit hymns known as the Rigveda (Wasson 1968). Among the physiologically active molecular constituents of *Amanita muscaria* are muscimol (a $GABA_A$-receptor agonist) and ibotenic acid (a glutamate receptor agonist) (Michelot & Melendez-Howell 2003).

A variety of plants from the family Solananceae – including *Atropa belladonna* (deadly nightshade), *Hyoscyamus niger* (henbane), *Mandragora officinarum* (mandrake),

Datura (devil's weed), and *Brugmansia* (angel's trumpet) – produce powerful alterations of consciousness characterized by intense hallucinatory activity. The major psychoactive chemicals in these plants are the tropane alkaloids atropine and scopolamine, compounds that have antagonist actions at muscarinic acetylcholine receptors, present throughout the brain and in the autonomic nervous system. These plants and the tropane alkaloids they contain are often characterized as deliriants, producing powerful hallucinations and severe mental confusion. They may also produce dangerous effects on the cardiovascular system, including acute tachycardia, hypertension, and cardiac arrhythmia. Nonetheless, they also have a history of medicinal, folkloric, and shamanic use throughout the world (Pendell 2010b).

Ketamine is a synthetic pharmaceutical drug used in human and veterinary surgical procedures. It is called a dissociative anesthetic because it brings about a loss of awareness of one's body. In sub-anesthetic doses it induces an altered state of consciousness that is uniquely and profoundly strange (Jansen 2001). Some say the ketamine-induced state provides a glimpse of a transcendental perspective on mind and reality – where one's consciousness becomes, in a weirdly palpable way, the fabric of reality itself. Recently ketamine has attracted interest for its potential utility as a rapidly-acting antidepressant (Ryan, Marta, & Koek 2014). How this property may relate to its psychedelic effects is not known. The primary neurochemical action thus far identified for ketamine is non-competitive antagonism at NMDA-type glutamate receptors, ionotropic channels found throughout the brain.

Regarding nitrous oxide (N_2O) – the intoxicant that so impressed William James many years ago – its primary identified neurochemical effects in the brain are antagonist actions at NMDA-glutamate receptors (similar to ketamine) and increasing the release of endogenous opioid peptides (Emmanouil & Quock 2007).

Inhalation of carbogen, another gas, can induce profound alterations of consciousness that may possess psychedelic qualities (James & Erowid 2007). The psychoactive component of carbogen is simply carbon dioxide, mixed with enough oxygen to not be a suffocation risk. 30% CO_2 and 70% O_2 is a standard combination (Meduna 1950). Effects on cerebral blood flow and on blood pH are likely factors in carbogen-induced altered states of consciousness. Similar mechanisms may be at work in the induction of powerful altered states via hyperventilation, a process that has been explored for millennia, from ancient practices in pranayama yoga to contemporary breath-work therapies (Grof & Grof 2010).

Finally, an increasing number of synthetic chemicals with psychedelic properties have appeared in recent years. These compounds have a spectrum of effects, some of which are along the lines of classical psychedelics. And there are many subtle and not-so-subtle differences (Shulgin & Shulgin 1991; Shulgin & Shulgin 1997). Those compounds that have been investigated have been found to interact with a great variety of neurotransmitter receptors (Ray 2010; Halberstadt & Geyer 2011).

Now, here is what I believe to be a very important point: how $5HT_{2A}$ and other receptors for serotonin – as well as receptors for dopamine, trace amines, acetylcholine, opioid peptides, glutamate, and GABA – are related to the profound alterations of consciousness associated with all these various plant, fungal, and chemical substances, is in many ways as obscure now as it was in the time of William James, more than a century ago. I suspect it will be necessary to look beyond molecular interactions with membrane receptors to account for the properties of psychedelics (and other psychoactive drugs as well). To begin with, many drug molecules enter the interior of the cell

where they doubtless have significant interactions that impact neuronal function. And there may be other factors at work, the nature of which we have little clue about at present. If the history of science is to be our guide, there will be surprises ahead. Neurobiological research with these substances and their effects on consciousness has barely begun!

Current Research with Psychedelics

During the 1950s and 1960s, interest in psychedelics within the nascent field of biological psychiatry was robust – both for their clinical utility in psychotherapy, and for what their effects might reveal about the nature of the human mind. As word got out about these substances, millions of people experienced their powerful effects, and the impact of psychedelics on the history of that era is considerable – on music, art, political action, innovation, and technology (Markoff 2005). But the complexity of these substances and their power to open the psyche proved too much for science and society to accommodate at that time. The first laws against LSD and other psychedelics began to appear in the US in the late 1960s, and in 1970 the Federal Controlled Substances Act declared all the classical psychedelics to be without medical utility (despite evidence to the contrary) and legally prohibited their use or possession in the United States. The following year, the United Kingdom instituted a similar ban with the Misuse of Drugs Act, and the United Nations Convention on Psychotropic Substances extended the ban to most of the world. What had been a highly regarded experimental and clinical research agenda, filled with great promise, was rapidly closed down and marginalized (Nutt, King, & Nichols 2013).

Some 20 years later, in the early 1990s, clinical and basic research using psychedelics with humans slowly began to reenter the scientific mainstream. Now, 20 years again after that, while these substances still remain legally prohibited, it has become increasingly possible to conduct human research. Perhaps even more importantly, such research is no longer considered marginal, and increasingly considered an attractive scientific and clinical endeavor.

The contemporary era of renewed human investigation with psychedelics includes studies of the physiological and phenomenological effects of DMT; psilocybin for anxiety associated with terminal cancer, and for the treatment of obsessive-compulsive disorder; LSD and MDMA for anxiety associated with life-threatening illness; MDMA for post-traumatic stress; psilocybin and LSD for severe headache; and ayahuasca, peyote, ibogaine, and psilocybin for addiction.

The use of legally banned drugs to treat medical and psychiatric conditions deserves some comment. While psychedelics are extremely powerful in their effects on the psyche, when used with care and respect they can be uniquely effective therapeutic agents. Psychedelics do not promote addictive use and the harms associated with use are frequently overstated (Nutt, King, & Nichols 2013). Recent epidemiological analyses indicate that use of classical psychedelics is not linked to mental health problems or suicidal behavior, and may instead be associated with reduced psychological distress and suicidality (Johansen & Krebs 2015; Hendricks et al. 2015). That's not to say that adverse reactions to these powerful substances do not occur, even under conditions of careful application – but such reactions are the exception rather than the rule when respectful attention is given to set and setting.

Importantly, the use of psychedelic therapy employs a very different model from that currently prevailing in psychiatric psychopharmacology. Contemporary psychiatric pharmacology largely focuses on the utility of long-term daily use of medications labeled as anti-depressant, anti-psychotic, mood-stabilizing, or anxiolytic. In contrast, psychedelic psychotherapy employs very limited (once, several times, or very sporadic) use of psychedelic substances to catalyze experiences that will have lasting therapeutic impact. Preparation, intention, and other aspects of set and setting are of great importance in this model.

Some of the most innovative ideas in the early 1960s regarding psychedelics and consciousness emerged from projects orchestrated by Timothy Leary and his collaborators. Among these projects was Walter Pahnke's "Good Friday experiment," which demonstrated an association between set, setting, and psychedelic chemical (in this case, psilocybin) in the production of mystical experience (Doblin 1991). This work from more than half a century ago provided inspiration for a more recent study demonstrating that psilocybin, administered to healthy subjects under conditions designed to encourage psychological exploration in a safe therapeutic environment, prompted experiences of a mystical nature that had lasting beneficial impacts (Griffiths et al. 2006; Griffiths et al. 2008). Currently underway are investigations of how psilocybin experiences and meditation practices may interact and impact one another.

Beginning in the 1990s, functional brain imaging methods began to be applied to understanding the basic neurobiology of psychedelics. Among these investigations was work done in Switzerland using positron emission tomography (PET) to measure changes in regional glucose metabolism (reflecting neural activity) following administration of various psychedelic agents, including psilocybin and ketamine (Vollenweider & Kometer 2010). Recent work in the United Kingdom has employed functional magnetic resonance (fMRI) and other imaging technologies with psilocybin (Carhart-Harris et al. 2012) and with LSD in humans (Carhart-Harris et al. 2016). Findings have been interpreted as changes in distributed neural networks that may indicate enhancement of unconstrained brain activity.

Thus, it is now possible to conduct carefully controlled human studies with psychedelics in laboratory settings, bringing to bear tools and techniques of contemporary molecular, cellular, and systems neuroscience, as well as sophisticated phenomenological inquiry to address what is happening as these agents catalyze profound transformation of consciousness. And though there continue to be considerable legal and societal obstacles, things are on track to continue to explore psychedelic medicines for the treatment of severe and often intractable conditions – anxiety associated with terminal illness, addiction, post-traumatic stress – as well as tools to increase psychological health. The momentum is strong, the science is solid, and there is reason to be optimistic that the future will see increasing attention to investigations of these remarkable materials as probes to the neurobiology and phenomenology of consciousness, and as powerfully effective therapeutic agents. As pioneering psychedelic researcher and psychotherapist Stanislav Grof wrote in the reissue of his classic 1980 book *LSD Psychotherapy*: "it does not seem to be an exaggeration to say that psychedelics, used responsibly and with proper caution, would be for psychiatry what the microscope is for biology and medicine or the telescope is for astronomy. These tools make it possible to study important processes that under normal circumstances are not available for direct observation" (Grof 2001, p. 12).

Coda

The shamanic use of psychedelic plants and fungi speaks to their long history of evoking mystical-type experiences. By "mystical" I mean evocative of profound feelings of sacredness, unity, and connection. Scholar of mysticism Paul Marshall put it this way:

> Perhaps more so than any other kind of experience, mystical experience invites us to question received assumptions about the nature of reality, the ways in which it can be known, and our relation to it. Mystics can feel as if they've looked behind the veil of appearances and caught sight of the nature of self, world, consciousness, time, and even the meaning of it all. While a traditional branch of philosophy called "metaphysics" has approached a similar set of concerns through discursive reasoning, mystical experience is said to involve a direct intuition, a special way of knowing or "gnosis" independent of the senses and rational analysis.
>
> *(Kelly, Crabtree, & Marshall 2015, p. 42)*

Within contemporary Western popular culture, Aldous Huxley is known for drawing attention to a connection between psychedelics and mystical experiences. His encounter with mescaline led to his writing *The Doors of Perception*, a book that became one of the ways knowledge of these powerful substances reached the general populace. In that little book Huxley advanced the idea that psychedelics may work in part by impacting a filtering capacity of the brain:

> According to such a theory, each one of us is potentially Mind at Large. But in so far as we are animals, our business is at all costs to survive. To make biological survival possible, Mind at Large has to be funneled through the reducing valve of the brain and nervous system. What comes out at the other end is a measly trickle of the kind of consciousness which will help us to stay alive on the surface of this particular planet.
>
> *(Huxley 1954, p. 23)*

That living beings may be conduits for something far more expansive, some "Mind at Large" or transcendental consciousness, is a notion that spans human history – from Plato, Plotinus, and William James in the West, to Patañjali, Abhinavagupta, and Sri Aurobindo in the East (Kelly, Crabtree, & Marshall 2015). That psychedelics may be one way of opening a door to some kind of transcendental consciousness certainly seems an idea worth exploring. However, such a notion challenges us to be open to explanatory frameworks that go well beyond our current biophysical models of mind and reality.

"No account of the universe in its totality can be final which leaves these other forms of consciousness quite disregarded. How to regard them is the question … At any rate, they forbid a premature closing of our accounts with reality" (James 1902, p. 388). The science of consciousness may be poised at the threshold of revolution, in that radical new perspectives may be required to get to the next level of insight concerning consciousness and its connection with the rest of reality. This is the kind of revolution where the framework of explanation before and after is vastly different. Revolutions of

this magnitude have taken place only a few times in the 500-year history of modern Western science: Copernicus, Kepler, Galileo, Newton, and the heliocentric cosmos; Darwin, biological evolution, and the interconnectedness of all life; Einstein and the relativity of space, time, matter, and energy; and quantum physics and the irreducibly uncertain properties of physical reality independent of measurement. While we are able to describe in molecular detail many processes inside living cells and inside brains, it is likely we are only just scratching the surface. Life is unfathomably complex, and living organisms have been refining their project here on Earth for billions of years. Just how it is that life is able to manifest consciousness is likely to amaze and surprise us again and again as we continue its study in the years, decades, and centuries to come.

See also 13 Anomalous experience; 15 Altered states: mysticism; 8 Panpsychism; 27 Physicalist panpsychism.

Further Readings

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