Fear and Loathing for Science: Hallucinogenic Plasticity

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Abstract

Hallucinogens have been used for centuries as spiritual aids and guidance. While there are any number of mind-altering substances, the classical hallucinogens are perceptually and molecularly distinct from other classes. 5-HT2a hallucinogenic ligands differentially regulate intracellular signaling, transcription processes, and cell excitability in the neocortex, leading to wide-ranging brain changes in the long and short term. The synthesis of LSD in 1938 and the subsequent rise of recreational drug use in the 60s cut short the flood of research on the hallucinogenic potential for treating anxiety, depression, pain, addictions, and compulsions, among other things. However, in recent years, researchers have begun to unravel the processes of plasticity underlying therapeutic processes.

Hallucinogens in Culture and History

Hallucinogens have maintained a presence in a variety of cultures through nearly all of human history, from *soma* in India to sun dried peyote cacti in the American southwest, Lithuanian marriage receptions with *amanita muscaria* (fly agaric) and vodka to the spiritual healing journeys of the San Pedro cacti curative cults high in the Andes mountains. Some historians theorize witches in Medieval Europe were merely under the influence of datura, henbane, mandrake, or belladonna, practicing pagan rites outlawed by the Christian church. The southern Bushmen of Dobe, Botswana absorb the active constituents of the plant *kwashi* through intentionally opened wounds, and Siberians can be found toasting fly agaric with blueberries over the fire[3]. Mind-altering substances have

a presence in seemingly every human culture [11]. While these hallucinogens have been traditionally used as spiritual tools, and continue to function as such (e.g. the Native American Church is licensed for peyote usage [11]), Albert Hoffman's synthesis of lysergic acid diethylamide (LSD) [1][2][3] in the 1930s set off twenty years of furious research in psychiatry into potential therapies relating to anxiety disorders, obsessive–compulsive disorders, depression, addiction, and sexual dysfunctions, among others. Many also focused on hallucinogens as a type of model psychosis, an easily induced and quantifiable form of schizophrenia. Admittedly, most of this research was primarily anecdotal, suffered from a lack of controls and followup, and had almost no ethical regulations in comparison to today's standards for any human-related experiment[24]. However, LSD synthesis also brought a host of highly potent compounds to a recreational audience, and the fierce political backlash in the United States unfortunately brought research to a grinding halt by the 1970s. Until the 1990s, hallucinogens existed primarily in religious ceremonies and as recreational drugs, and only very slowly have made their way into the line of scientific inquiry in a few highly regulated and prestigious laboratories.

With all of the cultural cachet of hallucinogens, one might think defining what exactly a hallucinogen is would be easy. However, in the layman's mind, and indeed much scientific literature, it is far from clear what is meant by 'hallucinogen', 'psychedelic', or even mind-altering. As it stands today, "hallucinogen" is a catchall term including tetrahydrocannabinol (THC), the active ingredient in marijuana, alongside toxic compounds like datura, which produces an anticholinergic delirium toxic in large doses[4], and the empathogen MDMA. Perceptual and molecular assessment indicate a number of different potential categorizations. The most basic definition is a substance inducing perceptual, somatic, and psychic changes: an altered state of consciousness [21].

[1] * - compounds highly selective for 5-HT2 receptors, and thus commonly used in scientific research
[2] MDMA is not strictly a hallucinogen, but does play a major role in public perception of psychoactive substances
[3] Some common psychoactive substances

Chemical	common names	chemical name
DOB*	brolamfetamine	2,5-dimethoxy-4-bromoamphetamine
DMT	psychoactive ingredient in a number of plants, notably ayahuasca	dimethlytryptamine
DOM*	Serenity, Tranquility, Peace (STP)	2,5-Dimethoxy-4-methylamphetamine
MDMA**	Molly, Ecstasy	(3,4-methylenedioxy-N-methylamphetamine
LSD	LSD, acid, lysergide	Lysergic acid diethylamide
DOI*	-	2,5-dimethoxy-4-iodoamphetamine

What is a Hallucinogen?

Altered states of consciousness (ASC) are hard to measure and quantify, differing as they do from person to person. Scales for retrospective analysis of ASC measure how much a given individual's [11]psychic state varies with respect to standard metrics. The Altered States of Consciousness scale measures response in ten categories, including experience of unity, complex imagery, changed meaning of percepts, and disembodiment [26]. Hallucinogens primarily mediate sensory input, typically without casting any psychically depressant or excitatory effects effects–they will not make an individual happy or sad through any direct activation of so-called "happy" receptors. This excludes the sometimes hallucinogen MDMA, which induces sensory effects along with empathogenic effects mediated by a unique psychopharmacology. However, hallucinogens are also not restricted to the triumvirate of LSD, psilocybin, and mescaline[21]

Hallucinogenic dissociatives like Ketamine or phencyclidine (PCP) were originally developed as anesthetics, and are characterized by altered perception (although not true hallucinations[4]) and feelings of dissociation from the environment[1]. Users may experience a dreamy, carefree state with impaired judgement and heightened enjoyment of sensory stimuli, while others experience panic and highly disordered, potentially dangerous thinking (i.e. improper risk assessment)[1]. The dissociatives carry CNS depressant risks of a slowed heartbeat and breathing rate, similar to opioids, and are NMDA-receptor antagonists.

The hallucinogenic deliriants include deadly nightshade (atropa belladonna), henbane, nutmeg, datura, mandrake, and a host of other members of the potato family. Potent anticholinergics, deliriants induce states of fever-like confusion, stupor, and a general inability to distinguish reality from fantasy. Toxic in large doses because of their activity at acetylcholine receptors and the subsequent risk to generalized motor functions like cardiac functions and breathing, deliriants often produce unwanted and unpleasant effects, making them one-time use drugs [4].

Both dissociatives and deliriants alter states of consciousness, but their mode of action (NMDA-antagonists and anticholinergics, respectively) differentiate them from the so-called classical hallu-

[4]A common misnomer. True hallucinations are images completely disconnected from any incoming stimuli. Hallucinations as induced by classical hallucinogens are typically distortions of salient stimuli–a complication of the visual input, rather than the creation of something new.

cinogens in both effect and long term results.

Classical Hallucinogens: Perceptually and Chemically

To narrow the working definition down from general perceptual, somatic, and psychic changes and eliminate most lingering ambiguities, the classical hallucinogens are also non-toxic and non-addictive, do not induce stupor or narcosis, and avoid excessive stimulation and autonomic side effects. They can also be characterized by their molecular structure and receptor binding affinity. The classic hallucinogens bind at 5-HT (serotonin) receptors, and are recognized by animals trained to discriminate DOM from vehicle[6]. Even beyond this, there are further subdivisions. Psilocin, the dephosphylated active ingredient in the psilocybin mushroom, is a structural analogue of 5-HT, and representative of the tryptamine/indoleamine hallucinogenic class. LSD is an ergoline, a subset of the tryptamine class with a phenethylamine backbone. Mescaline is the flagship molecule of the phenethylamines. These drug classes and their structural (dis)similarities are in figure 1 on the following page. While they do overlap in some respects, phenethylamines and indoleamines are structurally distinct. Nevertheless, they show similar clinical effects and cross tolerance, implying a shared pathway [2]. The classical hallucinogens, in simpler terms, are those compounds structurally and psychoactively similar to the semisynthetic LSD and the plant-derivatives psilocybin and mescaline.

Binding and Differential Signaling Mechanisms in Classical Hallucinogens

The classical hallucinogens all share an affinity for the 5-HT2a receptors. Numerous studies indicate the primary mediation of effects is through 5-HT2a agonist actions, and demonstrate the excellent correlation between the affinity of indoleamine/phenethylamine hallucinogens for 5-HT2 receptors and hallucinogenic potency [6].

Animal models for hallucinogenic assessment are often mice or rabbits, although rabbits are

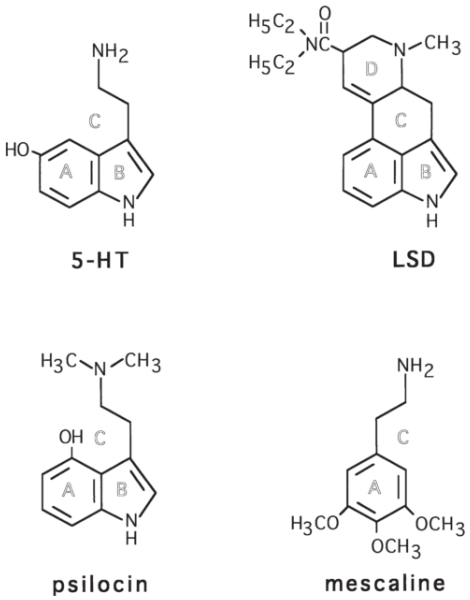

Figure 1: Figure 1. Structural formulae for serotonin (5-HT), LSD, mescaline, and psilocin. Chemical structures are in relation to the A, B, C, and D rings of LSD to emphasize common structural features: indolethylamine nucleus of 5–HT and psilocin, phenethylamine nucleus shared by LSD and mescaline. [2]

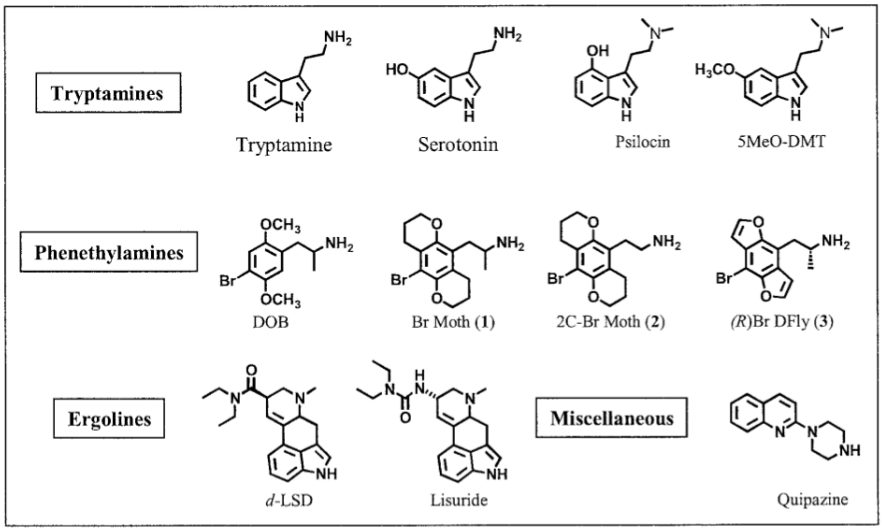

Figure 2: psilocin, 5MeO-DMT, DOB, *d*-LSD. Non-hallucinogens: Tryptamine, serotonin, molecules 1 2 and 3 of the phenethylamines, lisuride, and Quipazine

excessively susceptible to drug effects. In the classic differentiation task, mice are dosed with a known hallucinogen (typically DOI) and trained to respond when similar compounds arise. When dosed with classical hallucinogens, mice exhibit a consistent head twitch response (HTR), which can then used as a measure of hallucinogenic potency for other compounds. HTR is reliably elicited by a variety of proven hallucinogenic compounds, but is conspicuously absent with non-hallucinogens and in 5-HT2a-knock out mice, who demonstrate no behavioral reaction to hallucinogens [7].

However, hallucinogens are not the only ligands for 5-HT2a receptors. Intriguingly, structural snalogues to hallucinogens, like those seen in figure 2, fail to elicit HTR responses in mice despite binding to the same receptors. Eliciting the mechanisms of this discrepancy is an important indicator in determining how hallucinogens affect the brain and differentially regulate plasticity. One quantitative measure of differences in ligand signaling is the phospholipase release and accumulation as a results of an intracellular signaling cascade. While any activation of the 5-HT2a receptor sets offs both PLA2 (phospholipase A) release and PLC (phospholipase C) accumulation through heterotrimic G proteins, the efficiency of each cascade varies from compound to compound. [5]

[5] Although lisuride also binds to dopamine and 5-HT1A receptors, activation here does not functionally antagonize

Distinct ligands are able to induce preferential activation of the PLC or PLA2 pathways and their corresponding different intercellular signaling reserves (e.g. larger calcium reserves in PLA2 activation) [17]. For example, the non-hallucinogenic LSD analogue lisuride regulates phospholipase C in cortical neurons similarly to LSD, but the signaling response specific to LSD also requires a coactivation of Gi/o and Gq/11 proteins and activation of *Src*[6]. *Src* inhibition eliminates most of the behavioral response to LSD, indicating the additional pathway is likely requisite for hallucinogenic effects [7]. 5-HTa receptors are not universal across the brain, but rather are localized to specific locations both in the brain and on neurons.

Apical Dendrites of Cortical Pyramidal Neurons

5-HT2a receptors are localized to the apical dendrites of cortical pyramidal neurons and to a subset of dendritic spines and synapses[14]. Pyramidal cell bodies are found in all regions and layers II, III, V, and VI of the cerebral neocortex. The apical dendrites of these cells typically ascend into different layers– Layer VI apical dendrites extend to layer IV, and in the rest of the layers the apical dendrite extends to layer I. They are the only class of neuron projecting outside the cortex, act as the primary source of connection between different cortical areas, and are likely responsible for a good deal of information processing[25]. The activation of these far reaching dendrites by hallucinogenic compounds implies behavioral hallucinogenic results are not only excitability changes in small areas of the brain, but are the result of a network of interactions across many neuronal areas.

Excitatory and Inhibitory: Neuronal activity across the brain

Activation of layer V pyramidical neurons by hallucinogens lead to a wide range of altered ionic currents. Small and medium current changes occurred in HT2a receptor knockout mice, but large positive current changes (from the baseline neuron to after application) were only seen in wild-type LSD-treated neurons, and never with lisuride-treated neurons[7]. Cell clamp recordings demonstrate 5-HT increases the amplitude and frequency of excitatory post-synaptic currents (EPSCs).

2AR-dependent effects. [7]

[6]Gi/o protein-regulated phosphorylation networks involve other G protein subunit-mediated activation of Src

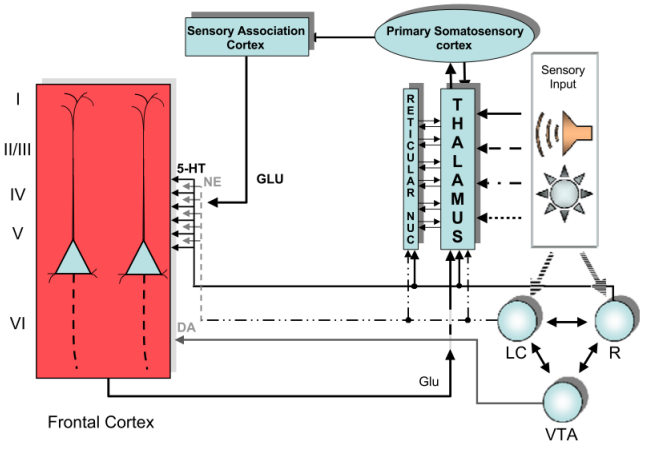

Figure 3: Model for potential brain interactions of 5-HT2a receptor agonists, adapted from Nichols 21

Essentially, hallucinogenic activation at 5-HT2a receptors makes neurons more excitable.

Stimulation of post-synaptic 5-HT2a receptors on glutamergic pyramidal cells in cortical layers V and VI projecting to layer V pyramidal neurons leads to an increase in extracellular glutamate levels. Extracellular glutamate leads to an activation of AMPA [7]and NMDA[8] receptors on the same cortical pyramidal neurons. AMPA receptors effect short-term changes in synaptic strength,and NMDA receptors regulate genes required for the long-term maintenance of synaptic changes [22]. Direct activation of 5-HT receptors and glutamergic AMPA and NMDA receptors also leads to increased expression of the growth-related brain-derived neurotrophic factor (BDNF) expression[30].

Increased excitability across brain areas leads to a set of functional interactions that together lead to hallucinogenic effects, summarized in Nichols' 2004 paper. A model of brain areas affected by 5-HT2a hallucinogenic agonist actions, either directly or indirectly, are represented in figure3. In the prefrontal cortex, serotonin receptors are localized on the apical dendrites of pyramidal cells in the deep layer IV and superficial layer V. The raphe nucleus (R) sends serotonin projections to forebrain structures, notably the frontal cortex. Hallucinogens reduce the firing rate of raphe cells, either by direct stimulation of inhibitory 5-HT1A receptors or by 5-HT2a receptor activation

[7]α-amino-3-hydroxy-5-methyl-4- isoxazole propionic acid
[8]N-methyl-d-aspartate

of inhibitory GABA interneurons. Cessation or reduction of raphe cell firing leads to a disruption of normal serotonergic activity, including reduced activation of inhibitory 5-HT1A receptors on cortical pyramidal axons. Incoming sensory information is processed through the thalamus, with modulation by the reticular nucleus of the thalamus, which has afferents from some thalamic nuclei and associated cortical areas. Many thalamic nuclei as well as the reticular nucleus express 5-HT2a receptors. Alterations in the firing mode of thalamic neurons are associated with dramatic changes in the neuron's responsiveness to peripheral stimuli. The locus couerulus (LC) and the ventral tegmental area (VTA) express 5-HT2a receptors and also receive pre-modified input from the raphe, and then send it elsewhere. The LC sends noradrenergic projections to both thalamus and cortex, and hallucinogens potentiate burst firing in LC neurons in response to novel stimuli. The VTA is the origin of dopaminergic cells, and are depolarized by activation of 5-HT2a receptors, which would potentially lead to enhanced release of DA in cortex. he somatosensory and sensory association cortex, responsible for cortical-thalamic timing regulation as well as merely processing sensory information, also expresses 5-HT2a receptors, a potential explanation for hallucinogenic time distortion[21]. 5HT2A receptors are also found in a variety of other areas, including the olfactory bulb, claustrum, nucleus accumbens, olfactory tubercle, and facial nucleus, although these have yet to be implicated in hallucinogenic functioning [2].

Short term plasticity

Gene Expression

Apart from the immediate sensory effects mediated by changes in post-synaptic potentials, hallucinogens set off a chain of genetic and cellular modifications classically associated with growth and development. Different 5-HT2a receptor ligands set off different signaling cascades, and in turn this affects transcription rates of certain genes. Acute LSD application increases *C-fos* expression twofold in the prefrontal cortex, hippocampus, and midbrain of rats. *Arc* expression was upregulated fivefold in the prefrontal cortex,but not the hippocampus or midbrain [20]. In a separate study, the transcriptome fingerprints (TFPs) of different 5-HT2aR agonists showed distinctive and repro-

ducible signatures. LSD and DOI activate a significant head-twitch response in mice (an indicator of hallucinogenic potential), in contrast to LHM[9], which is chemically and pharmacologically close to LSD, but fails to induce similar psychological and behavioral effects. Three genes, *c-fos*, *N-10*, and *I-κba* , showed a similar modulation by all three agonists. The genes *egr-1*, *egr-2,* and *period-1* were unaffected by LHM, but were similarly activated by the structurally dissimilar yet hallucinogenic agonists DOI and LSD [8]. Hallucinogens also regulate genes in a way distinctive to each drug, DOI significantly downregulated *lynB* and *egr-3*, and both DOI and the non-hallucinogenic LHM downregulated STY kinase. The different patterns of cellular signaling induced by agonists translate to a unique transcriptome fingerprint, perhaps explaining long term behavioral changes as a result of hallucinogenic experiences[8].

The upregulated genes are predominantly growth and activity genes. *C-fos* expression is associated with recent increases in neuronal firing, and increases in hippocampal *c-fos* seem to be an important mediator of activity-dependent neuroplasticity [28]. *I-κba* is part of a family of transcription factors controlling expression of the NF-KB protein, which functions as a first responder protein in immune, inflammatory, and acute phase responses [29]. Both *c-fos* and *I-κba* are upregulated in response to most, if not all, 5-HT2a receptor agonists, implying a non-specific activation. More interesting, however, are the genes upregulated only in response to hallucinogens. *Egr-1* (early growth factor 1) regulates transcription of nerve growth factors. Genes regulated by *egr-1* include synapsin I and II (shown to significantly reverse synaptic depression and have a restorative effect on the density of synaptic vesicles), neurofilament light chain (a major component of cell cytoskeleton, and provide support for axonal radial growth), and a whole host of other factors related to synaptic plasticity and growth. *Egr-1 also* interacts with other transcription factors like cAMP and *c-fos*, and is augmented following long-term potentiation [15]. *Egr-2* is a transcription factor in the same family, related to myelin-producing genes and processes *[5]Period-1* is named for its circadian properties, but synaptic transmission through per-expressing cells is most likely to be required during retrieval of LTM [23]. *Arc* is a actin-cytoskeleton related gene, and encodes a protein that is critical for memory consolidation. *Arc* also regulates synaptic strength through multiple mechanisms and

[9]lisuride hydrogen maleate

is involved in most forms of synaptic plasticity [16].

The transcriptional changes engendered by hallucinogenic binding of 5-HT2a receptors are likely not responsible for the immediate sensory effects, which can be attributed to excitability changes.. They are, however, relevant to the anatomical changes of dendritic spine size and longer-term downregulation of 5-HT2a receptors.

Downregulation and dendritic growth

Tolerance to LSD and its fellow hallucinogens develops remarkably quickly. Rats treated chronically with LSD showed a significant 44% reduction in LSD lever responding (from 91 to 51%), while rats treated chronically with saline showed no change in LSD lever responding, indicating tolerance development [9]. A number of experiments have indicated a significant decrease in 5-HT2a receptors in response to hallucinogens, highly correlated with tolerance buildup. Daily LSD, DOB, or DOI treatment selectively decreases 5-HT2 receptor density, rapid desensitization and down-regulation of central 5-HT2 receptors is observed following repeated treatment of rats with DOM. Tolerance to the discriminative stimulus effects of DOI in rats was correlated with down-regulation of 5-HT2a receptors [21]. Gresch, using the same drug dosing regimen that produced tolerance to the stimulus effects of DOI, produced significant reductions in the density of brain 5-HT2a receptors in the cortex and claustrum [9].

Time-lapse imaging of neurons undergoing DOI perfusion (1 M) for up to 60 min showed a transient increase in spine size after a half hour, and recovery to control size after an hour. PAK, the molecular target of activated Rac, is a regulator of the actin cytoskeletal rearrangements underlying dendritic spine remodeling, and activation of a Rac/PAK pathway induces larger spines. DOI treatment for 30 min resulted in a dose-dependent increase in PAK phosphorylation (indicating activity) in cortical neuron homogenates, consistent with the spine increase seen in the imaging[14].

The Good, The Bad, and The Mystical: Long-term Hallucinogenic effects

The Neutral

Hallucinogenics of all kinds can leave permanent effects on their subjects, for better or for worse. Popular culture is rife with talk of 'bad trips'–terrifying descents into a hallucinated Hell, endless pain and suffering, schizophrenic breaks, violent and self-destructive behavior. Clinically, there is documentation of flashbacks and persistent revisiting of unpleasant hallucinogenic effects. However, on the whole, the long term effects of various hallucinogens are positive, or at least, in the spirit of the Hippocratic oath, do no harm.

Halpern compared long-term (>100 uses) religious peyote users to a control group and a former alcoholic group on a battery of nonverbal and psychological tests. Next to Navajos with minimal substance use, the peyote group showed no significant deficits on the RMHI or any neuropsychological measures, whereas the former alcoholic group showed significant deficits on every scale of the RMHI (Rand Mental Health Inventory) and on two neuropsychological measures. While no peyote use and any neuropsychological test measure approached significance, greater lifetime peyote usage associated with significantly better scores on five of the nine RHMI scales[13].

Do no harm

Before benefits, there is the incidence of hallucinogen persisting perception disorder (HPPD) to consider. HPPD has 3 component parts in today's definition, according to the DSM-IV: re-experiencing one or more of the perceptual symptoms experienced while hallucinogenically intoxicated; clinically significant distress or impairment in social, occupational, or other important areas of functioning due to the revisited symptoms; and not due to a general medical condition (such as anatomical lesions and infections of the brain, visual epilepsies) or better accounted for by another mental disorder (schizophrenia, psychoses, dementia, etc). Much of the research on what is now called HPPD is more than 20 years old, when ethics were less of a concern and studies often did not feature appropriate controls, definition of terms, similar methodologies, and lacked many details required to formally diagnose HPPD[12]. A review of much of the research on flashbacks and long-term

effects came away with conclusions to inform any hallucinogen uses. First, flashbacks have been defined too many times in the literature to have any functional meaning left. Even with the data restricted to reports similar to the diagnosis of HPPD as defined by the DSM, the studies vary widely in estimates of prevalence–from essentially no users experiencing lingering effects to as high as 77%. There is also a lack of accounting for alternate factors like psychotic disorders prior to ingestion or other potentially traumatizing non-related incidents. Controlled laboratory evidence and assessment of prevalence also has serious flaws, as controlled settings see less long lasting negative effects because of selection bias of non-psychotic, fully informed, and not overdosed patients [12]. Essentially, while persisting negative effects are genuine, they tend to be isolated and rare, and are often associated with patients already suffering from trauma or psychological disorders.

Therapeutic applications and mysticism

Why should serious academics and well-balanced individuals bother with risking a bad trip? On a purely life affirming note, an experimental assessment with psilocybin was rated as having "substantial personal and spiritual significance" and sustained positive changes in mood, attitudes, and behavior attributed to the mystical-type psilocybin experiences. At 14 months, ratings were undiminished and consistent with changes rated by community observers [10]. A pooled analysis assessing the short- and long-term dose related effects of psilocybin noted profound changes in mood, perception, thought and self-experience in the short-term, which most subjects described as pleasurable, enriching, and non-threatening. Strong short-term effects, such as dysphoria, anxiety, and/or panic, occurred only in the two highest dose-conditions, in a relatively small proportion of subjects, and acute adverse drug reactions were managed by providing interpersonal support. Follow-up questionnaires indicated no subsequent drug abuse, persisting perception disorders, prolonged psychosis or other long-term impairment of functioning in any subjects [27]. These studies, along with others drawing similar conclusions, suggest the administration of some hallucinogens to healthy, high-functioning, and well-prepared subjects in context of a carefully monitored positive research environment is an acceptable level of risk, in light of the potential benefits.

In positive research environments, with proper preparation, hallucinogens are beginning to show

serious potential for therapies in a number of areas. Their anatomical and transcriptional changes may play a potential role in a number of therapies.

The speedy downregulation of 5-HT2a receptors as a results of hallucinogens could play a role in their efficacy in treating anxiety, depression, and chronic pain. Post-mortem samples of patients with major depression show increased 5-HT2a receptor density, and a reduction in density when clinical anti-depressants set in. Downregulation of 5-HT2a receptor in mice through non-hallucinogenic means corresponded with reduced anxiety-like behavior [30]. Past research suggests LSD reduces the intensity of chronic pain, and may assist in coping with the anxiety induced by terminal diagnoses because of the mystical-type experiences induced by hallucinogens.

Anecdotal evidence indicates a number of potential directions to explore. Ibogaine, a hallucinogenic LSD analogue, has demonstrated remarkable efficacy in treating heroin, cocaine, and methamphetamine addictionMaisonneuve and Glick [18]. The first clinical trial of psilocybin as an OCD treatment showed acute reduction of symptoms with no other significant adverse affects for more than 24 hours [19].

Conclusion & Future Research

The mechanisms of hallucinogenic plasticity have only begun to be explored. While the Schedule I ban on nearly all forms of naturally-occuring or synthesized hallucinogens has severely hindered research, the past ten years have experienced an upsurge in hallucinogenically-related publications. Classical hallucinogens have yet to show any risk to autonomic functioning, unlike alcohol, tobacco, and cough syrup, which are all available as over the counter drugs. Psychologically, there is some incidence of long-term persisting negative effects, but this has not been seen in any clinical trials with proper controls and therapy options. Hallucinogenic regulation of gene transcription and synaptic density may be important regulators of their efficacy in treating a variety of psychological disorders and anxiety, and significantly improve the quality of life for terminally ill patients.

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