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ASCP Corner

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Therapeutic Potential of Psychedelics in the Treatment of Psychiatric Disorders, Part 1: Psychopharmacology and Neurobiological Effects

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Psychedelics (Greek: "mind manifesting"), also referred to as hallucinogenic drugs, are a group of compounds that produce various (often profound) psychological effects characterized by altered states of perception, thoughts, feelings, and consciousness. Since the early 2000s, there has been a resurgence in clinical research into psychedelics with increasing interest recently among clinicians and patients to harness their therapeutic potential in treating psychiatric disorders. A review of the literature with a critical eye that may inform psychiatrists of the current state of the evidence is hence timely. This article is the first in a 2-part series[1] on the psychopharmacology and therapeutic effects of psychedelics. In it, we provide a review of the psychopharmacology and neurobiological mechanisms underlying the use of psychedelic-assisted psychotherapy, with a focus on psilocybin, (±)-3,4-methylenedioxymethamphetamine (MDMA), lysergic acid diethylamide (LSD), and ayahuasca. While mescaline, a naturally occurring hallucinogen in peyote; salvinorin A, found in the plant *Salvia divinorum*; and ibogaine, an alkaloid found in the West African plant iboga, are other psychedelics with considerable therapeutic interest, the paucity of human clinical studies precluded their inclusion in this brief review. While there is no standard definition for "psychedelics," these compounds produce profound alterations in the perception of reality and mystical experiences. Compounds such as ketamine, a dissociative anesthetic, are not typically included in this class.

Pharmacology

The "classical" psychedelics, consisting of indolamines (psilocybin), alkaloids (*N,N*-dimethyltryptamine [DMT], the active constituent contained in ayahuasca), and ergolines (LSD), act primarily via serotonin 5-HT_{2A} receptor agonism. MDMA, a phenethylamine, acts via release of presynaptic serotonin and to a lesser extent norepinephrine and dopamine through interactions with the corresponding monoamine transporter, including trace amine-associated receptor 1 (TAAR1) and vesicular monoamine transporter 2 (VMAT2). These compounds have varied pharmacokinetics and pharmacodynamics[2] (Table 1). Serotonergic hallucinogens produce "psychedelic" effects that are indistinguishable from each other, consistent with a shared primary mechanism of action.[2] The typical effects include enhanced sociality, feelings of closeness to others, openness to new experiences, emotional empathy, trust, feelings of bliss, audiovisual synesthesia, derealization, depersonalization, profound mystical experiences characterized by feelings of boundlessness, enhanced introspection and occasionally anxiety, fear/panic, dysphoria, paranoia, and auditory hallucinations.[9–11] MDMA, described as an "entactogen" (Greek: "touching within"; ie, increases empathy and feelings of closeness) and a psychostimulant (producing euphoria, anxiolysis, and a sense of inner peace), does not produce intense hallucinations as seen with classical psychedelics.[7] Psychedelics are generally well tolerated at clinically relevant doses, although side effects are common (Table 2). In nonclinical/recreational settings, adverse psychiatric effects have been reported in 40% of users, with 7.6% reporting enduring psychological symptoms.[12] There are few pharmacokinetic drug interactions, but the short half-lives of psychedelics decrease the risk for accumulation even in the setting of metabolic inhibition. Of greater relevance are pharmacodynamic drug interactions, such as those with serotonergic drugs (eg, selective serotonin reuptake inhibitors, dextromethorphan), which may increase the risk for serotonin syndrome.

In animal studies, psychedelics elevate glutamate levels in the cortex, increase regionally specific gene expression of brain-derived neurotrophic factor and immediate-early genes, and promote both synaptogenesis and neuroplasticity through a TrkB- and mTOR-dependent mechanism.[13] Long-term administration of psychedelics has been shown to cause significant transcriptional changes that last long after stopping them.

Psilocybin

Psilocybin, derived from mushrooms belonging to the genus *Psilocybe*, and psilocin, its active metabolite, are indolamines. Recent studies have shown that psilocybin has effects on brain functional connectivity.[14] Its effects include reducing negative affect and amygdala response to emotional faces at 1 week, with enduring changes in resting state functional connectivity (RSFC) at 1 month,[15] along with reducing activity in the default mode network (DMN) (including the subgenual cingulate cortex) in healthy individuals[16] and causing changes in synaptic plasticity.[13] Contrary to the finding in healthy individuals, psilocybin was associated with increased resting state connectivity within the DMN between the ventromedial prefrontal cortex and the bilateral inferior-lateral parietal cortex after 2 psilocybin treatments in treatment-resistant depression patients and was predictive of clinical response 5 weeks posttreatment.[17]

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Table 1. Pharmacology

Pharmacodynamics	Pharmacokinetics
Psilocybin (*O*-phosphoryl-4-hydroxy-*N*,*N*-dimethyltryptamine)	
5-HT_{2A} agonism[3] Various other 5-HT receptors (eg −7, −2B, −1A autoreceptor, and −6 subtypes)[3]	Dephosphorylation to active metabolite psilocin by alkaline phosphatase and nonspecific esterases[3] MAO, ADH, hydroxyindole oxidases[3] Glucuronidation of metabolites[3]

Route	PPB	t_{max}	Onset	$t_{1/2}$	Duration	f_e	F
Oral	80%[3]	90 min	20–40 min	2.5 h	4–6 h	3%–10%	50%

LSD (lysergic acid diethylamide)	
5-HT_{2A} partial agonism[4] TAAR-1 agonism 5-HT_{1A} agonism, various other 5-HT receptors (−1B, 1D, −5A, −6, and −7) Mixed DA agonism and antagonism[4]	CYP enzymes (unknown)[4] Glucuronidation of metabolites[4]

Route	PPB	t_{max}	Onset	$t_{1/2}$	Duration	f_e	F
Oral	65%–90%[4]	1–2.5 h	30–45 min	2.9 h	9–12 h	<1%	100%

Ayahuasca (*Banisteriopsis caapi* and *Psychotria viridis* or *Diplopterys cabrerana*)	
DMT: 5-HT_{2A} agonism[5] β-carbolines: 5-HT_{2A} agonism, reversible MAO_A-I[5] Other effects: DMT: TAAR and sigma-1 agonism β-carbolines: multiple, including DAT inhibition and imidazoline I_2 agonism[5]	Multiple chemical constituents, including the CYP2D6 substrate and β-carboline harmine and MAO substrate DMT[5]

Route	PPB	t_{max}	Onset	$t_{1/2}$	Duration	f_e	F
Oral[a]	NA	1–2 h[5]	20 min	1 h	4–5 h	NA	NA
Smoked DMT	NA	15 min	20–40 s	15 min	5–20 min	NA	NA

MDMA ((±)-3,4-methylenedioxymethamphetamine)	
Intracellular sequestration of MDMA and reuptake inhibition: NET > SERT > DAT[6] VMAT2 inhibition, TAAR-1 agonism Weak, reversible MAO_A-I[8] H_1, M_1, α_2 antagonism[7]	Nonlinear kinetics[7] Major: CYP2D6, COMT[7] Minor: CYP1A2/2B6/3A4[7] Sulfurylation and glucuronidation of metabolites[7]

Route	PPB	t_{max}	Onset	$t_{1/2}$	Duration	f_e	F
Oral	34%[7]	2 h	1–2 h	8–9 h	4–6 h	15%	Good

[a]DMT is orally active only when coadministered with a MAO-I.
Abbreviations: 5-HT = serotonin (5-hydroxytryptamine), ADH = aldehyde dehydrogenase, COMT = catechol-*O*-methyltransferase, CYP = cytochrome P450, DAT = dopamine (DA) transporter, DMT = *N*,*N*-dimethyltryptamine, F = bioavailability, f_e = fraction excreted unchanged in the urine, k_i = inhibition constant, MAO-I = monoamine oxidase (MAO) inhibitor, NA = not available, NET = norepinephrine transporter, PPB = plasma protein binding, SERT = serotonin transporter, $t_{1/2}$ = half-life in plasma, TAAR = trace amine associated receptor, t_{max} = time to maximum plasma levels after oral administration, VMAT = vesicular monoamine transporter.

Table 2. Common Adverse Drug Reactions

Drug	Reactions
Psilocybin (*O*-phosphoryl-4-hydroxy-*N*,*N*-dimethyltryptamine)[3]	Mydriasis, mild hypertension and tachycardia, dizziness, nausea, anxiety, drowsiness, hyperreflexia, mild headache
LSD (lysergic acid diethylamide)[4]	Mydriasis, mild hypertension and tachycardia, hypophagia, dizziness, nausea, mild headache
Ayahuasca (*Banisteriopsis caapi* and *Psychotria viridis* or *Diplopterys cabrerana*)[5]	Mild hypertension, poorly tolerated gastrointestinal effects (nausea, vomiting, diarrhea)
MDMA ((±)-3,4-methylenedioxymethamphetamine)[7]	Mydriasis, mild hypertension and tachycardia, hypophagia, bruxism, fatigue, xerostomia, hyperthermia

LSD

First synthesized in 1938 by Albert Hofmann, LSD is an ergot alkaloid derivative that acts as a 5-HT_{2A} partial agonist and 5-HT_{1A} agonist with additional dopaminergic activity at moderate-high doses (75–200 μg).[4] LSD, like other psychedelics, acutely increases plasma concentrations of cortisol, prolactin, oxytocin, and epinephrine.[18] Neuroimaging studies show that LSD acutely increases global functional connectivity[19] and reduces left amygdala and right medial prefrontal cortex reactivity to fearful faces.[20] LSD's subjective hallucinatory effects are associated with increased functional thalamic connectivity with the insula and the right fusiform gyrus.[21] Similar to psilocybin, LSD decreases DMN integrity, which correlates with ratings of ego dissolution.[22]

Ayahuasca

Ayahuasca is the most popular name for an Amazonian decoction used in religious ceremonies prepared from the vine *Banisteriopsis caapi* (which contain β-carbolines such as harmine) and leaves of *Psychotria viridis* (which contains DMT).[23] While harmine is a monoamine oxidase inhibitor that prevents peripheral metabolism and increases oral bioavailability of DMT, ayahuasca's psychedelic effects are primarily due to DMT.[24] Structurally similar to melatonin and serotonin, endogenous DMT and its metabolite, 5-OH DMT, are hypothesized to be responsible for dreams, creativity, and other mystical experiences.[25] Interestingly, in animals, DMT has been shown to produce fear extinction and antidepressant effects with cellular and behavioral responses similar to ketamine.[23]

MDMA

Also known as "ecstasy," MDMA's exact mechanism as a psychotherapy adjunct for treating posttraumatic stress disorder is unknown, but its entactogenic effects may lower emotional barriers, dampen conditioned fear responses, and improve

introspection to facilitate engagement with and extinction of traumatic memories during psychotherapy. Neuroimaging findings in healthy individuals include decreased neural activation of the left amygdala in response to angry vs neutral faces[26]; lower activation of the left anterior temporal lobe and greater activation of the superior frontal gyrus/dorsal medial prefrontal cortex, which correlated with worst autobiographical memories being perceived less negatively[27]; decreased RSFC between the prefrontal cortex and hippocampus; and increased RSFC between the hippocampus and amygdala.[28]

The Current State of the Field and Future Directions

While significant progress has been made in the understanding of the psychopharmacologic and neurobiological effects of psychedelics, several questions remain unanswered. For example, although 5-HT_{2A} agonism has been shown to be important for the "psychedelic" effects of these compounds, it is unclear whether the therapeutic effects are also mediated via 5-HT_{2A} receptors or by other mechanisms, such as 5-HT_1, VMAT2, and TAAR-1. The understanding of the neurobiological effects of psychedelics is based on studies with small sample sizes in predominantly healthy adults. Replication and validation of these findings in larger studies in both normal and disease/pathological states are important. Furthermore, the mechanisms underlying the adverse outcomes observed in nonclinical settings remain to be understood.

The dose-response relationship between psychedelics and their therapeutic effects is not well established. Whether a linear dose-response relationship exists or if there is a narrow therapeutic window has yet to be determined. Additionally, while the therapeutic effects of psychedelics are thought to last up to 6 months following a single exposure, the mechanisms underlying these long-lasting effects remain to be deciphered.

Conclusions

Classical serotonergic psychedelics have commonalities in their pharmacology, psychological effects, and mechanism of action via 5-HT_{2A} agonism. MDMA, however, has a distinct and complex neuroreceptor profile. Psychedelic and therapeutic effects may be mediated by more than one mechanism. The effects of psychedelics on brain functional connectivity and synaptic plasticity offer additional mechanisms that warrant further research.

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