

Lysergic Acid Diethylamide and Psilocybin Revisited

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The past decade brought the beginnings of a renaissance in research on psychedelic drugs. Two articles in this issue of *Biological Psychiatry* signify that the resurrection of this long-ignored topic has begun to mature and bear at least the promise of fruit. In the early 1970s, the onset of the “War on Drugs” brought with it a near-total hiatus in serious research on psychedelic drugs, especially in the United States. The resumption of credible work in this area has come from Switzerland, where many of the original pioneering studies were initiated in the 1950s and 1960s. The two articles presented here address the phenomenology and underlying mechanisms of action for two classic psychedelic drugs: lysergic acid diethylamide (LSD) and psilocybin. Schmid *et al.* (1) examined the effects of the most famous psychedelic, LSD, which was discovered in Basel, Switzerland, by Hofmann in 1943 (2). Schmid *et al.* demonstrated that a robust dose of LSD was feasible for studies in healthy volunteers and that it markedly reduced sensorimotor gating as indexed by prepulse inhibition of the startle response (PPI). This disruption of PPI by LSD mimicked not only the disruption reported in parallel experiments in rodents but also the similar deficit in PPI observed in patients with schizophrenia. Kraehenmann *et al.* (3) combined state-of-the-art imaging methods with validated clinical rating scales and a well-established affect modulation task to characterize the effects of psilocybin on positive mood and identify circuitry subserving these effects. Hofmann also identified psilocybin as the active principle in *Psilocybe* mushrooms (“magic mushrooms”) in 1958 (2). Largely as a result of the pioneering work of the Vollenweider group in Zurich, Switzerland, psilocybin became the foremost practical laboratory tool suitable for use in experimental medicine studies in healthy human volunteers. The article by Kraehenmann *et al.* (3) reflects the maturation of this group’s research by building on their studies addressing the behavioral, emotional, psychophysiological, electrophysiological, and brain imaging alterations resulting from administration of psilocybin, ketamine, and other psychoactive drugs in healthy humans. Many of these pharmacologic studies were conducted in parallel with assessments in psychiatric patient populations. Kraehenmann *et al.* (3) used functional magnetic resonance imaging to confirm that acutely administered psilocybin led to a decrease in right amygdala reactivity to negative stimuli that was associated with a psilocybin-induced reduction in emotional reactivity to negative stimuli. Furthermore, this change in the amygdala response was related to a psilocybin-induced enhancement of positive mood.

The demonstration that LSD disrupts PPI in healthy subjects has several implications, as discussed by Kraehenmann *et al.* (3). As summarized elsewhere (2), the original idea that

LSD intoxication may provide a model of psychosis that could help identify substrates of psychotic disorders such as schizophrenia was vitalized by Swiss researchers a year before serotonin was suggested to be a neurotransmitter in 1948. In the mid-1950s, Woolley and Shaw hypothesized that serotonin could be involved in the etiology and treatment of schizophrenia. Although American psychiatric researchers largely dismissed LSD as a useful model psychosis, European scientists continued to explore this model, leading to Janssen’s development of the atypical antipsychotic risperidone as a compound that blocked the behavioral effects of amphetamine and LSD in animals. The report by Schmid *et al.* (1) that acute administration of LSD mimics the deficit in PPI seen in patients with schizophrenia and some other psychotic disorders (4) helps to validate retroactively animal studies showing that LSD disrupts PPI by acting as a 5-hydroxytryptamine 2A (5-HT_{2A}) receptor antagonist (5,6). It is now recognized that 5-HT_{2A} agonists disrupt not only PPI but also more controlled forms of inhibition as well as attention and that all these effects are prevented by a 5-HT_{2A} antagonist (7). One wonders how much earlier we might have developed atypical antipsychotics with strong 5-HT_{2A} receptor antagonist effects if more investigators had used model psychosis paradigms involving 5-HT_{2A} agonists.

One long-standing mystery regarding the mechanism of action of psychedelic drugs was that lisuride, a congener of LSD, is not hallucinogenic despite being a 5-HT_{2A} agonist. More recent studies have shown that although lisuride disrupts PPI in rodents as does LSD, it does so by a dopaminergic mechanism rather than via its 5-HT_{2A} agonist action (6). Work with lisuride indicates that agonist-directed trafficking, or functional selectivity, may explain why not all 5-HT_{2A} agonists are hallucinogenic in humans. It will be interesting in future studies to assess the effects of lisuride on PPI in healthy human volunteers.

The article by Schmid *et al.* (1) provides other important conclusions. First, despite sympathomimetic effects that warrant cautious monitoring, experimental studies with robust doses of LSD are feasible when subjects are carefully selected, settings are nonthreatening, and investigators follow the subjects beyond the extended duration of the drug effect. Drug effects clearly persisted in several subjects for 16 hours after ingestion. The robustness of the 200- μ g dose of LSD was clear; scores on symptom rating scales far surpassed the scores produced by other psychedelic drugs such as psilocybin. The high scores on measures of empathogenic effects, which are more commonly associated with the nonhallucinogenic serotonin releaser methylenedioxymethamphetamine, were another surprising result. At a biological level, LSD

SEE CORRESPONDING ARTICLES ON PAGES 544 AND 572

increased plasma oxytocin in addition to expected increases in stress-related markers. The authors opine that these observations may indicate some utility for LSD treatment in psychotherapeutic settings.

Previous studies in Vollenweider's laboratory had used behavioral and electrophysiologic assessments to demonstrate that the psychedelic psilocybin may have antidepressant properties insofar as it increased positive moods, while decreasing the emotional and neural reactions to visually presented negative stimuli. Based on strong evidence in the literature showing amygdala involvement in the affective response to negative images, Kraehenmann *et al.* (3) tested and confirmed the hypothesis that the previously observed behavioral and neural activity changes were attributable to psilocybin-induced activation of the right amygdala. Particularly striking was the observation that the attenuation of amygdala reactivity to negative stimuli was significantly correlated with scores on the positive affect subscale of the Positive and Negative Affect Scale. The authors discussed prior evidence from their group and related preclinical work in rodents strongly supporting the belief that these affective effects of psychedelics are attributable to 5-HT_{2A} agonist actions. Kometer *et al.* (8) used self-report and event-related potential measures of responses to emotional cues such as facial expressions to show that psilocybin enhanced positive moods, while attenuating the impact of negative emotional stimuli, and that both alterations were prevented by the 5-HT_{2A} antagonist ketanserin.

As with the rapid and lasting antidepressant effects of acutely administered ketamine, a glutamate receptor antagonist often characterized as a psychotomimetic, some reports in the literature had prompted the speculation that acute experiences with psilocybin might also have antianxiety, antidepressant, or positive mood effects that outlive the duration of drug action. As discussed by Kraehenmann *et al.* (3), a safety study in patients with terminal cancer found reductions in anxiety and increases in positive mood 6 months after a single administration of psilocybin (9). Similarly, Griffiths *et al.* (10) demonstrated that healthy volunteers given psilocybin acutely reported striking spiritual and mystical experiences that appeared to have positive sequelae over many months. Given such reports and the strong empirical data provided by Kraehenmann *et al.* (3) identifying neural circuits subserving positive mood effects of psilocybin, it would be interesting to examine whether psilocybin might have rapid and potentially lasting antidepressant effects in patients with severe depression.

In conclusion, these two articles describing rigorous and sophisticated examinations of the effects of two 5-HT_{2A} agonists, LSD and psilocybin, in healthy human volunteers offer the promise of a resurgence of psychedelic drug research to understand mechanisms underlying their actions and gain insights into normal and abnormal brain function. After nearly half a century in which the field was largely constrained to a small cadre of preclinical researchers studying these mysterious drugs in necessarily simple animal paradigms, it is refreshing to see the reopening of this work in humans. Nevertheless, it is unclear whether this promise will be fully materialized. Although the Swiss National Science Foundation supported the work of Schmid *et al.* (1), the work of Kraehenmann *et al.* (3) and most of the related studies from the

Vollenweider laboratory were supported by visionary private foundations instead of governmental agencies. In the United States, support from the National Institutes of Health for research on psychedelic drugs has diminished from programs operating in several basic science laboratories in the recent past to only three currently listed in NIH RePORTER (<http://projectreporter.nih.gov/reporter.cfm>). The promise of this line of research is just beginning to be realized; thus, it will be important for adequate research funding to be identified to extend this work further and answer the question whether or not there are therapeutically beneficial effects of this intriguing family of compounds.

Acknowledgments and Disclosures

This work was supported by National Institute on Drug Abuse Grant No. R01 DA002925-31 ("Monoamine and Hallucinogen Effects on Rodent Behavior") and the U.S. Department of Veterans Affairs VISN (Veterans Integrated Service Networks) 22 Mental Illness Research, Education, and Clinical Center ("Functional Outcome in Chronic Psychosis").

I thank Dr. Athina Markou for helpful comments on drafts of this manuscript.

In the past 3 years, MAG has received consulting compensation from Abbott Laboratories, Dart NeuroScience, H. Lundbeck A/S, Neurocrine Biosciences, Omeros Corporation, Otsuka America Pharmaceutical, and Sunovion Pharmaceuticals and holds an equity interest in San Diego Instruments.

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Received Aug 6, 2015; accepted Aug 6, 2015.

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