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Acute Effects of Lysergic Acid Diethylamide in Healthy Subjects

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ABSTRACT

BACKGROUND: After no research in humans for >40 years, there is renewed interest in using lysergic acid diethylamide (LSD) in clinical psychiatric research and practice. There are no modern studies on the subjective and autonomic effects of LSD, and its endocrine effects are unknown. In animals, LSD disrupts prepulse inhibition (PPI) of the acoustic startle response, and patients with schizophrenia exhibit similar impairments in PPI. However, no data are available on the effects of LSD on PPI in humans.

METHODS: In a double-blind, randomized, placebo-controlled, crossover study, LSD (200 μg) and placebo were administered to 16 healthy subjects (8 women, 8 men). Outcome measures included psychometric scales; investigator ratings; PPI of the acoustic startle response; and autonomic, endocrine, and adverse effects.

RESULTS: Administration of LSD to healthy subjects produced pronounced alterations in waking consciousness that lasted 12 hours. The predominant effects induced by LSD included visual hallucinations, audiovisual synesthesia, and positively experienced derealization and depersonalization phenomena. Subjective well-being, happiness, closeness to others, openness, and trust were increased by LSD. Compared with placebo, LSD decreased PPI. LSD significantly increased blood pressure, heart rate, body temperature, pupil size, plasma cortisol, prolactin, oxytocin, and epinephrine. Adverse effects produced by LSD completely subsided within 72 hours. No severe acute adverse effects were observed.

CONCLUSIONS: In addition to marked hallucinogenic effects, LSD exerts methylenedioxymethamphetamine-like empathogenic mood effects that may be useful in psychotherapy. LSD altered sensorimotor gating in a human model of psychosis, supporting the use of LSD in translational psychiatric research. In a controlled clinical setting, LSD can be used safely, but it produces significant sympathomimetic stimulation.

Keywords: Adverse effects, Hormones, LSD, Prepulse inhibition, Subjective effects, Sympathomimetic effects

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Lysergic acid diethylamide (LSD) is a prototypical classic hallucinogen (1,2). The psychotropic effects of LSD were discovered in 1943 by Hofmann in Basel (3). In the 1950s–1970s, LSD was initially used as an experimental tool ("psychotomimetic") to study psychotic-like states and model psychosis (4,5) and as an adjunct in "psycholytic psychotherapy." It has also been investigated for the treatment of alcoholism (6), addiction (7), cluster headache (8), and anxiety associated with terminal illness (9–11). Today, LSD is used illicitly for recreational (personal or spiritual) purposes. The lifetime prevalence of LSD use among adults is 6%–8% (12,13). Despite the widespread recreational use, no experimental scientific pharmacologic studies have been conducted with LSD in the last 40 years, until recently (14). After the initial psychiatric investigation by Stoll (15), several case reports and studies in the 1950s and 1960s described aspects of the psychological effects of LSD (5,16–18). However, these studies were not performed according to current research standards and did not include control conditions or the systematic characterization of psychotropic effects. Many studies also sought to describe the psychotomimetic effects of LSD but were not designed to measure any positive subjective effects. Modern experimental studies with hallucinogens in humans resumed in the 1990s with *N*-*N*-dimethyltryptamine (DMT; also known ayahuasca) (19–22), ketamine (22–24), and psilocybin (25,26), but not with LSD. More recently, LSD and psilocybin have been evaluated in pilot therapeutic studies as treatments for anxiety in patients with life-threatening diseases (11,27). Because of the continued popularity of LSD as a recreational drug and renewed interest in its therapeutic use (11,28), we re-examined the acute response to LSD in healthy subjects. To allow for a better characterization of the subjective effects of LSD, we used psychometric instruments that have been used with other psychotropic drugs, including hallucinogens, empathogens, and stimulants (21,22,29–32).

Serotoninergic hallucinogens, including psilocybin, DMT, and LSD, elicit mostly visual perceptual disturbances that resemble perceptual disturbances observed in early schizophrenia (22,33–35). Hallucinogens also induce alterations in information processing that are similar to those observed in

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schizophrenia. Specifically, prepulse inhibition (PPI) of the acoustic startle response serves as an operational measure of sensorimotor gating that can be assessed in animals and humans (36). In schizophrenia, PPI is impaired in prodromal states and early phases (36–39), and hallucinogens such as LSD acutely disrupt PPI in animals (40–45). In animals, PPI serves as a preclinical model of schizophrenia (46). The effects of LSD on sensorimotor gating function have not yet been explored in humans and were tested in the present study. We hypothesized that LSD would produce alterations in waking consciousness and impair PPI. Additionally, no data are available on the acute autonomic and adverse effects of LSD, and the endocrine effects of LSD in humans are unknown. Up-to-date clinical safety data are mostly missing. Because of the continued popularity of LSD as a recreational drug and interest in its therapeutic use, we also examined the acute somatic and endocrine response to LSD.

METHODS AND MATERIALS

Participants

We recruited 16 healthy subjects (8 men, 8 women; mean age ± SD, 28.6 ± 6.2 years; range, 25–51 years) by word of mouth or an advertisement placed on the web market platform of the University of Basel. All subjects provided written informed consent and were paid for their participation. Additionally, we considered the safety recommendations for high-dose hallucinogen research (47,48). The participant characteristics are described in detail in Supplement 1. Seven subjects had used a hallucinogen one to three times, and another four subjects had prior experience with methylenedioxymethamphetamine (MDMA) (two to four times).

Study Design

A double-blind, placebo-controlled, crossover design was used with two experimental test sessions in balanced order. The washout periods between sessions were at least 7 days. The study was conducted in accordance with the Declaration of Helsinki and International Conference on Harmonization Guidelines in Good Clinical Practice and approved by the Ethics Committee of the Canton of Basel, Switzerland, and Swiss Agency for Therapeutic Products (Swissmedic). The administration of LSD to healthy subjects was authorized by the Swiss Federal Office for Public Health, Bern, Switzerland. The study was registered at ClinicalTrials.gov (NCT01878942).

Drugs

Administration of LSD was in a single absolute dose of 200 μg, corresponding to a dose of 2.84 ± .13 μg/kg body weight (mean ± SEM; range, 2.04–3.85 μg). The same dose was used in LSD-assisted psychotherapy in a clinical study (11). The dose was within the range of doses taken for recreational purposes and expected to induce robust effects in humans (1). The drug preparation is described in Supplement 1.

Study Procedures

The study included a screening visit with the study physician, a separate psychiatric interview, an additional visit with the study physician for familiarization, two 25-hour test sessions, and an end-of-study visit. The sessions were conducted in a calm laboratory environment. Only one research subject and one or two investigators were present during the test sessions. The test sessions began at 8:15 AM. A urine sample was taken to verify abstinence from drugs of abuse, and a urine pregnancy test was performed in women, and all subjects underwent baseline measurements. LSD (200 μg) or placebo was administered at 9:00 AM. The outcome measures were repeatedly assessed for 24 hours. A standardized lunch and dinner were served at 1:30 PM and 5:30 PM, respectively. The subjects were under constant supervision by the study physician until 1:00 AM. The subjects were never alone during the first 16 hours after drug administration, and the investigator was in a room next to the subject for up to 24 hours. The subjects were sent home the next day at 9:30 AM.

Subjective Drug Effects

Subjective measures included scores on the 5 Dimensions of Altered States of Consciousness (5D-ASC) scale (29,49), visual analog scales (VASs) (50), the Adjective Mood Rating Scale (AMRS) (51), and the Addiction Research Center Inventory (ARCI) (31). The 5D-ASC scale is designed to be used retrospectively and was administered 24 hours after drug administration to rate the peak drug effects. The VASs were administered repeatedly for up to 24 hours to assess drug effects over time. The AMRS and ARCI were administered before and 3, 10, and 24 hours after drug administration. The procedures are described in detail in Supplement 1.

Acoustic Startle Response Measurement

The eye-blink component of the acoustic startle response was measured using an electromyographic startle system (EMG-SR-Lab; San Diego Instruments, San Diego, California) as described in detail elsewhere (36) and in Supplement 1. Briefly, the session included 16 pulse-alone stimuli (115 dB) and 32 similar pulse trials that were preceded by a 20-msec prepulse (86 dB) and an interstimulus interval (ISI) of 30, 60, 120, or 2000 msec, resulting in four prepulse trial conditions.

Cardiovascular, Autonomic, Adverse, and Endocrine Effects

Cardiostimulant (blood pressure and heart rate), autonomic (body temperature and pupillary function), psychomotor performance, endocrine measures (plasma cortisol, prolactin, oxytocin, norepinephrine, and epinephrine), and adverse effects were measured as described in Supplement 1.

Data Analysis

The data were analyzed using STATISTICA Version 12 software (StatSoft, Inc, Tulsa, Oklahoma). Peak or peak change from baseline values were determined for repeated measures. Data were analyzed using repeated-measures analysis of variance (ANOVA), with drug (LSD vs. placebo) as the within-subjects factor. The PPI data were analyzed using repeated-measures ANOVA, with drug and trial condition (30, 60, 120, and 2000 msec) as within-subjects factors, followed by direct