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Acute effects of LSD on circulating steroid levels in healthy subjects

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ABSTRACT

Lysergic acid diethylamide (LSD) is a serotonin 5-hydroxytryptamine-2A ($5\text{-}HT_{2A}$) receptor agonist that is used recreationally worldwide. Interest in LSD research in humans waned after the 1970s, but the use of LSD in psychiatric research and practice has recently gained increasing attention. LSD produces pronounced acute psychedelic effects, but its influence on plasma steroid levels over time have not yet been characterized in humans. The effects of LSD (200µg) or placebo on plasma steroid levels were investigated in 16 healthy subjects using a randomized, double-blind, placebo-controlled cross-over study design. Plasma concentration-time profiles were determined for 15 steroids using liquid-chromatography tandem mass-spectrometry. LSD increased plasma concentrations of the glucocorticoids cortisol, cortisone, corticosterone, and 11-dehydrocorticosterone compared with placebo. The mean maximum concentration of LSD was reached at 1.7h. Mean peak psychedelic effects were reached at 2.4h, with significant alterations in mental state from 0.5h to >10h. Mean maximal concentrations of cortisol and corticosterone were reached at 2.5h and 1.9h, and significant elevations were observed 1.5-6h and 1-3h after drug administration, respectively. LSD also significantly increased plasma concentrations of the androgen dehydroepiandrosterone but not other androgens, progestogens, or mineralocorticoids compared with placebo. A close relationship was found between plasma LSD concentrations and changes in plasma cortisol and corticosterone and the psychotropic response to LSD, and no clockwise hysteresis was observed. In conclusion, LSD produces significant acute effects on circulating steroids, especially glucocorticoids. LSD-induced changes in circulating glucocorticoids were associated with plasma LSD concentrations over time and showed no acute pharmacological tolerance.

INTRODUCTION

Lysergic acid diethylamide (LSD) was discovered in 1943 and is the prototypic serotonergic hallucinogen (1, 2). LSD was used in psychiatric research in the 1950s to 1970s to study psychotic-like states (i.e., model psychosis) and as an adjunct to psychotherapy (1) before its widespread recreational use. Today, LSD is still frequently used for personal and spiritual purposes. Additionally, renewed interest has been seen in the use of LSD in psychiatric research (3) and practice (4). Pharmacologically, LSD mainly acts as an agonist at serotonin 5-hydroxytryptamine-1 (5-HT_1) and 5-HT_2 receptors, but it also interacts with dopamine D_1, D_2, and D_3 receptors and adrenergic α_1 receptors (2). In contrast to such stimulants as amphetamines or cocaine, LSD does not interact with monoamine transporters (2). In humans, LSD induces alterations in perception, methylenedioxymethamphetamine (MDMA)-like empathogenic mood effects, and moderate sympathomimetic stimulation (3).

Many psychoactive substances activate the hypothalamic-pituitary-adrenal (HPA) axis, leading to the release of adrenocorticotropic hormone (ACTH) and glucocorticoids (5, 6). However, limited data have been reported on the effects of LSD on the HPA axis. In rats, LSD increased 17-hydroxy-ketosteroid and 17-ketosteroid levels in urine, consistent with HPA axis activation (7), but effects on circulating corticosterone could not be shown (8). LSD was reported to increase cortisol levels in zebrafish (9). Early studies in humans found that LSD increased 17-ketosteroid excretion in urine (10, 11), but effects on circulating steroid levels were not investigated. LSD also blunted the normal increase in 17-ketosteroid after ACTH administration (10). We recently found that LSD significantly increased plasma cortisol 180 min after LSD administration in humans (3), also consistent with HPA axis activation. However, we previously determined only the concentrations of cortisol and not of other steroids and only up to 180 min (3) despite the much longer effects of LSD. A more comprehensive analysis of the effects of LSD on circulating levels of different steroids and including full time courses is still missing.

Corticosteroids, androgens, and progestogens may all contribute to or modulate psychotropic drug actions (12, 13). For example, amphetamine or MDMA-induced increases in plasma cortisol levels were associated with subjective drug effects (14, 15), and stress-induced increases in plasma cortisol levels correlated with euphoric responses to amphetamine (16). Testosterone plays a role in social behavior (17) that is enhanced by MDMA (18). Testosterone and progesterone both reduced cocaine self-administration in female rhesus monkeys (19), and progesterone is known to be associated with reductions of subjective responses to and the use of psychostimulants in women (13, 20, 21). Plasma dehydroepiandrosterone (DHEA) levels correlated with the subjective response to MDMA (14). Increases in DHEA and progesterone were also observed after γ-hydroxybutyrate administration (22).

Glucocorticoids are involved in the stress response and the modulation of behavior. In humans, inactive cortisone and active cortisol are the main glucocorticoids (23). Inactive 11-dehydrocorticostrone and active corticosterone (i.e., the major glucocorticoids in rodents) are present at lower concentrations than cortisone and cortisol in human plasma. However, corticosterone, which also has additional mineralocorticoid properties, presents a higher brain/plasma concentration ratio than cortisol (24). Mineralocorticoids are involved in the regulation of sodium absorption and blood pressure (25), and they also play a role in modulating the immune response (26). 11-Deoxycortisol is a precursor of cortisol (27). Aldosterone is the most important mineralocorticoid. 11-Deoxycorticosterone is a precursor of corticosterone and aldosterone and has mineralocorticoid activity (28).

To characterize the influence of LSD on plasma steroid levels, we newly evaluated the acute effects of LSD on the plasma concentrations of a series of steroids over 24 h in healthy subjects. We also explored the effects of LSD on a wide range of other steroids not previously measured. The plasma LSD concentration-steroid effect response curves over time were also plotted and compared with the LSD exposure-psychotropic effect relationship. The psychotropic effects of LSD were previously published (3) and selected effects were included here to determine associations with steroid levels.

MATERIALS AND METHODS

Study design

The study used a double-blind, placebo-controlled, cross-over design 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). All of the subjects provided written informed consent after being given written and oral descriptions of the study, the procedures involved, and the effects and possible risks of LSD administration.

Participants

Sixteen healthy subjects (eight men and eight women; mean age ± SD: 28.6 ± 6.2 years; range: 25-51 years) were included. The exclusion criteria were pregnancy, personal or family (first-degree relative) history of psychotic or major affective disorder, regular use of medications, chronic or acute physical illness, lifetime prevalence of illicit drug use > 10 times (except for tetrahydrocannabinol), illicit drug use within the last 2 months, and illicit drug use during the study as reported in detail elsewhere (3). The subjects were asked to abstain from excessive alcohol consumption between test sessions and particularly limit their use to one drink on the day before the test sessions. Additionally, the participants were not allowed to drink caffeine-containing liquids after midnight before the study day. Three subjects were light smokers (< 10 cigarettes/day) and were told to maintain their usual smoking habits but not smoke during the sessions. We performed urine drug tests at screening and before each test session using TRIAGE 8 (Biosite, San Diego, CA, USA). The safety recommendations for high-dose hallucinogen research were followed (29).

Study procedures

The test sessions began at 8:00 AM. A urine sample was taken to verify abstinence from drugs of abuse, and a pregnancy test was performed in women. An indwelling intravenous catheter was placed in an antecubital vein for blood sampling, and the subjects completed baseline measurements. A single dose of LSD (200 µg) or placebo was administered orally at 9:00 AM. A standardized lunch and dinner were served at 1:30 PM and 5:30 PM, respectively. The subjects were sent home the next day at 9:30 AM after the 24 h blood sample collection. The sessions were conducted in a calm laboratory environment. The subjects did not engage in any physical activity and were resting in hospital beds during the test session. Blood samples for the analysis of plasma steroid hormone levels were collected in lithium heparin tubes 1 h before and 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, and 24 h after LSD or placebo administration. Blood samples were immediately centrifuged, and plasma was rapidly stored at -20°C. Plasma LSD concentrations were determined using liquid-chromatography tandem mass-spectrometry (LC-MS/MS; (30). The pharmacokinetics of LSD have been reported previously (31), and LSD concentrations are included herein to describe the LSD exposure-steroid response effect relationship. The subjective and autonomic effects of LSD were also recorded in this study and have been reported previously (3). The subjective effects of LSD over time were repeatedly recorded at the times of blood sampling using visual analog scales (VAS) as previously reported (3, 31) and the VAS item “any subjective drug effect” which reflects the overall subjective response is also presented in the figures herein for comparisons with the effects of LSD on steroid concentrations (Fig. 3 and Fig. S1). VASs included “any subjective drug effects”, “good drug effects”, “bad drug effects”, “fear”, and “stimulation”. VASs were presented as 100-mm horizontal lines (0-100%) marked “not at all” on the left and “extremely” on the right (3, 32).

Steroid quantification

Plasma steroid hormone levels (cortisol, cortisone, corticosterone, 11-dehydrocorticosterone, 11-deoxycorticosterone, aldosterone, DHEA, DHEA sulfate [DHEAS], Δ4-androstene-3,17-dione [androstenedione], testosterone, 11-deoxycortisol, progesterone, 5α-dihydrotestosterone, androsterone, and 17α-hydroxyprogesterone) were determined as previously described with minor adaptations (6). A detailed description of the materials, procedure, and method validation is included in the Supplemental Data.

Briefly, for solid-phase extraction, 700 µl of each plasma sample was mixed with 100 µl of protein precipitation solution (0.8 M zinc sulfate in water/methanol [50/50, v/v]) that contained deuterium-labeled aldosterone, corticosterone, androstenedione, androsterone, 5α-dihydrotestosterone, and testosterone as internal standards and diluted to a final volume of 1 ml with water. The samples were incubated in a thermoshaker for 10 min at 4°C with thorough shaking (1300 rotations per minute). The samples were then centrifuged for 10 min at 16,000 × relative centrifugal force at 4°C, and 700 µl of the supernatants was transferred to Oasis HBL SPE cartridges, preconditioned with methanol and water. After washing once with 1 ml of water and twice with 1 ml of methanol/water (10/90, v/v), the steroids were eluted with 1 ml of methanol and evaporated to dryness. The samples were then reconstituted in 25 µl of methanol. The steroids were separated and quantified by ultra-pressure LC-MS/MS (UPLC-MS/MS) using an Agilent 1290 UPLC coupled to an Agilent 6490 triple quadrupole mass spectrometer equipped with a jet-stream electrospray ionization interface. Analyte separation was achieved using a reverse-phase column (Waters ACQUITY UPLC BEH C18, 1.7 µm, 2.1 × 150 mm). Mass Hunter software (Agilent Technologies) was used for data acquisition and analysis. As described in detail in the supplement, the variation coefficient was <15% and accuracy between 85 and 115% tested at three concentrations for all analytes. The recovery of control samples was in the range of 80-120%.

Drugs

Gelatin capsules that contained 100 µg LSD (D-lysergic acid diethylamide hydrate; Lipomed AG, Arlesheim, Switzerland) and corresponding placebo capsules were prepared with authorization from the Swiss Federal Office for Public Health. LSD was administered in a single absolute dose of 200 µg, corresponding to a dose of 2.8 ± 0.1 µg/kg body weight (mean ± SEM). The same dose was previously used in LSD-assisted psychotherapy in a clinical study (4). The dose was in the upper range of doses that are taken for recreational purposes and expected to induce robust effects in humans (1).

Statistical analyses

To determine differences between LSD and placebo, maximum concentration (C_{max}) values and areas under the concentration-time curve (AUCs) were compared for each steroid using repeated-measures analysis of variance (ANOVA), with drug (LSD *vs*. placebo) as the within-subject factor. Gender differences were determined by including gender (male *vs*. female) as a between-subject factor in the ANOVA. To test how long the subjective and endocrine responses last over time, data were also analyzed using two-way ANOVAs with drug and time as factors and Tukey tests were used for post hoc comparisons between corresponding time points. C_{max} was determined directly from the concentration-time curves. AUC values were determined from time 0.5 h to 10 h (AUC_{10}) using the trapezoidal method. The LSD exposure-steroid concentration response relationships were explored by plotting the LSD response as a function of steroid concentration after LSD administration minus the individual time-matched concentration after placebo as a function of LSD plasma concentrations at each time point (hysteresis curves). Correlations between mean LSD concentrations and mean LSD-induced subjective (5 scales) or endocrine responses (cortisol and corticosterone) over time as well as correlations between subjective and endocrine responses over time (n=12 time points) within the 16 subjects were then analyzed using Spearman's rank correlations. The level of significance was set to $P < 0.05$. Seventeen correlations were tested, giving a Bonferroni-corrected statistical threshold of

P<0.003. The statistical analyses were performed using STATISTICA 12 software (StatSoft, Tulsa, OK, USA).

RESULTS

The plasma concentration-time curves of the different steroid hormones after LSD and placebo administration are shown in Fig. 1 and 2. Peak steroid concentrations, total steroid exposure over time (AUC_{10} values), and statistics are presented in Table 1. LSD significantly increased the plasma concentrations of the glucocorticoids cortisol, cortisone, corticosterone, and 11-dehydrocorticosterone compared with placebo (Fig. 1B-E). LSD also significantly increased the sums of cortisol+cortisone and corticosterone+11-dehydrocorticosterone and the cortisol/cortisone and corticosterone/11-dehydrocorticosterone ratios (Table 1), indicating elevated glucocorticoid production. LSD had no effect on plasma concentrations of the cortisol precursor 11-deoxycortisol (Fig. 1A), the mineralocorticoid aldosterone (Fig. 1G), or the moderate mineralocorticoid 11-deoxycorticosteone (Fig. 1F). LSD significantly increased plasma concentrations of DHEA compared with placebo (Fig. 2A) and also increased the plasma exposure (AUC_{10} but not C_{max}) of androstenedione compared with placebo (Fig. 2C). In contrast, LSD did not alter plasma concentrations of the androgens DHEAS (Fig. 2B), testosterone (Fig. 2D, F), 5α-dihydrotestosterone, or androsterone (Table 1). Similarly, LSD had no effect on plasma concentrations of the progestogens progesterone (Fig. 2G) and 17α-hydroxyprogesterone (Fig. 2E). As expected, testosterone levels were higher in men than in women, but no sex differences in testosterone levels in response to LSD were found compared with placebo. Similarly, no other drug and gender interaction effects on any of the steroid levels were observed.

LSD exposure-steroid concentration response relationships are shown in Fig. 3. Pharmacokinetic data on LSD from the present study have been published elsewhere in detail (31). The C_{max} of LSD was reached 1.7 ± 1 h (mean ± SD) after LSD administration (Fig. 3A, B). The peak psychotropic effect was reached 2.4 ± 0.8 h, with significant

alterations in mental state from 0.5 to 10 h after LSD administration (Fig. 3A, B). Maximum concentrations of cortisol (Fig. 3C, D) and corticosterone (Fig. 3E, F) were reached at 2.5 ± 0.8 h and 1.9 ± 0.5 h (mean ± SD), and significant elevations were observed 1.5-6 h and 1-3 h after LSD administration, respectively. Thus, plasma levels of corticosterone increased more rapidly and fell more rapidly back to baseline levels compared with cortisol levels (Fig. 3E, F). Counterclockwise hysteresis was observed for subjective "any drug effects" and cortisol, consistent with an initial delay between increases in plasma LSD concentration and drug effects that was attributable to drug absorption/distribution up to 2.5 h (Fig. 3B, D). After maximal drug effects were reached at 2.5 h, the psychotropic effects and changes in plasma cortisol levels decreased slowly, paralleling the steady decrease in the plasma levels of LSD (Fig. 3A, C) and presenting a close concentration-effect relationship up to 24 h (Fig. 3B, D). The average plasma level of LSD was strongly correlated with the average subjective "any drug effects" and the average level of cortisol over time (R_s=0.94, P<0.001 and R_s=0.97, P<0.001, respectively). The relationship between "subjective any drug effect" and circulating glucocorticoids was explored by plotting the LSD-induced subjective "any subjective drug effect" as a function of changes in the plasma concentrations of cortisol and corticosterone (Fig. 3G, H). After LSD administration, subjective drug effects increased together with plasma corticosterone levels but more rapidly than plasma cortisol levels. At 1 h after LSD administration, 80% of the average maximal subjective drug effect was reached, with more than 50% of the maximal corticosterone response but less than 50% of the maximal cortisol response. Thus, the psychotropic effects of LSD seemed to appear faster than the LSD-induced changes in plasma cortisol levels. Nevertheless, the average subjective "any drug effect" was closely related to the levels of cortisol and corticosterone (R_s=0.97, P<0.001 and R_s=0.90, P<0.001, respectively). LSD produced pronounced subjective "good drug effects" and "stimulation", but induced only small increases in subjective "bad drug effects" and "fear" compared with placebo as reported previously (3). Average subjective "good drug effects" and "stimulation" were both strongly associated with the plasma levels of LSD over time (R_s=0.88, P<0.001 and R_s=0.84, P<0.001, respectively). Average "good drug effects" and

"stimulation" were both also associated with the plasma levels of cortisol (R_s=0.93, P<0.001 and R_s=0.82, P<0.001, respectively) and corticosterone (R_s=0.86, P<0.001 and R_s=0.84, P<0.001, respectively). In contrast, LSD-induced "bad drug effects" or "fear" did not correlate with LSD-induced increases in cortisol or corticosterone over time. Supplemental Fig. S1 shows the concentration-effect curves of MDMA (125 mg) for "any drug effects", cortisol, and corticosterone based on our previous study in 16 healthy subjects (6, 33) for comparisons with the concentration-effect curves of LSD (Fig. 3B, D, F). The MDMA concentration-effect relationships for the psychotropic effects and glucocorticoid responses exhibited clockwise hysteresis, indicating acute pharmacological tolerance (Supplemental Fig. S1A-C). Consistently, the average subjective "any drug effects" did not significantly correlate with the average plasma levels of MDMA over time. After MDMA administration, the subjective drug effects increased faster and particularly decreased faster than the plasma levels of cortisol (Supplemental Fig. S1D) and corticosterone (Supplemental Fig. S1E; i.e., clockwise hysteresis). Thus, MDMA-induced changes in plasma glucocorticoid levels over time did not well reflect the psychotropic effects of the drug, in contrast to LSD, in which no tolerance was observed.

DISCUSSION

The present study provided insights into the acute effects of LSD on the plasma levels of a series of steroids in healthy humans. LSD increased circulating glucocorticoid levels, whereby the levels of both inactive 11-dehydrocorticosterone and cortisone and active corticosterone and cortisol were elevated compared with placebo, indicating HPA axis stimulation. The LSD-induced changes in circulating cortisol and corticosterone had, in contrast to the glucocorticoid response to MDMA, a close relationship with both the plasma concentrations of LSD and psychotropic response to LSD. No clockwise hysteresis in the LSD concentration-effect plots was observed, thus indicating no acute tolerance to the effects of LSD on glucocorticoid concentrations or subjective drug effects, in contrast to the pronounced acute tolerance observed with MDMA. LSD also significantly increased plasma

concentrations of the androgens DHEA (AUC_{10}, C_{max}) and androstenedione (AUC_{10}), but the concentration of testosterone was unaltered, and the ratio of active to inactive androgens (testosterone/androstenedione) decreased. Other androgens, as well as progestogens and mineralocorticoids, were unaffected by LSD.

The LSD-induced relative increase in corticosterone was greater than the increase in cortisol. The brain penetration of corticosterone is greater compared with cortisol because of differential transport by P-glycoprotein at the blood-brain barrier (24). Thus, the effect of LSD on brain corticosterone concentrations may be more prominent. Additionally, the LSD-induced changes in circulating corticosterone in the present study also more closely reflected psychotropic alterations over time, in which plasma cortisol levels increased later in time than the subjective effects of LSD after drug administration.

Stimulation of the HPA axis by LSD has previously been demonstrated in animals (7, 9) and in a preliminary study in humans (10). The present study in humans provided a more comprehensive analysis of plasma concentration-over-time profiles up to 24 h after drug administration and of a series of different steroids. LSD is a prototypic serotonergic hallucinogen that mainly acts as a potent serotonin 5-HT_1 and 5-HT_2 receptor agonist. It also less potently binds to dopamine D_{1-3} and adrenergic α_1 receptors but does not inhibit monoamine transporters (2, 34). In the present study, LSD also increased plasma levels of prolactin (3), which is a marker of increased serotonergic activity (35, 36). Similar to LSD in the present study, the hallucinogen psilocybin increased plasma levels of cortisol in healthy humans along with increases in prolactin and ACTH (37). Importantly, psilocybin (psilocin) activates 5-HT receptors similar to LSD, but does not exhibit relevant binding to D_{1-3} and α_1 receptors unlike LSD (34), indicating that HPA axis activation by serotonergic hallucinogens including LSD involves mainly 5-HT receptors. Consistently, it has been shown that 5-$HT_{2A/C}$ receptors stimulate ACTH and corticosterone release and activate CRF-expressing cells in the hypothalamic periventricular nucleus (38, 39).

Many psychotropic drugs activate the HPA axis (5). Acute administration of serotonin transporter inhibitors (35, 40) but not dopamine transporter inhibitors (6, 41, 42) increases plasma cortisol levels, indicating that serotonin rather than dopamine mediates HPA axis stimulation. Cocaine inhibits presynaptic serotonin, dopamine, and norepinephrine reuptake transporters and increases ACTH and cortisol in humans (12, 43). Amphetamine activates the norepinephrine and dopamine but not serotonin systems and increases cortisol (15, 42), although to a lesser extent than the serotonergic drugs LSD and MDMA. One speculation is that the stimulant-induced increase in cortisol may depend on dopamine-mediated HPA axis stimulation (15, 43). However, the stimulatory effects of amphetamines on ACTH secretion are mediated by adrenergic receptors (44) and not by dopamine (45). Additionally, methylphenidate activates the dopamine system and produces stimulation and euphoria that are similar to those produced by amphetamines (33, 46), but methylphenidate did not increase plasma cortisol levels (6, 42) or only to a small extent (46). Furthermore, the MDMA-induced increase in circulating cortisol was reduced by pharmacologically blocking the MDMA-induced release of serotonin and norepinephrine (47, 48) but not when dopamine release was blocked (41). The greater effects of amphetamine on cortisol release compared with methylphenidate are thus likely attributable to its greater noradrenergic *vs*. dopaminergic properties compared with methylphenidate (42, 49, 50). Nonetheless, the present study showed that stimulation of the serotonin system by LSD increased cortisol levels similarly to MDMA, which has more amphetamine-type properties and stimulates both the serotonin and norepinephrine systems.

Stimulation of the HPA axis involves serotonin and norepinephrine systems (45). Similar to LSD, the serotonin and norepinephrine releaser MDMA increased the plasma concentrations of the glucocorticoids cortisol, corticosterone, and 11-dehydrocorticosterone (6). Unlike LSD and MDMA, methylphenidate, which activates dopamine and norepinephrine systems but not the serotonin system, did not significantly alter plasma steroid levels in humans (6, 42), further supporting a role for serotonin receptors in drug-induced HPA axis

stimulation. Unexpectedly, the glucocorticoid response was more pronounced after LSD administration than after MDMA administration (6). This is consistent with the greater psychotropic response to LSD compared with MDMA (33); Supplemental Fig. S1A). In contrast, MDMA produced more stimulant-type effects, including greater increases in blood pressure and heart rate (33). The greater glucocorticoid response after LSD compared with MDMA indicates that the direct serotonergic stimulation of postsynaptic 5-HT_1 and 5-HT_2 receptors by LSD similarly or even more effectively stimulated the HPA axis compared with the release of both serotonin and norepinephrine by MDMA (48). The relatively similar time course of the glucocorticoid response and psychotropic effects of LSD, together with the greater glucocorticoid and psychotropic response to LSD compared with MDMA, raise the issue of whether the subjective effects of LSD contribute to or further enhance HPA axis stimulation by LSD. We observed a close relationship between LSD-induced subjective drug effects and changes in plasma corticosterone levels. Associations between amphetamine-induced increases in cortisol and subjective arousal and euphoria have been previously reported (15, 42). The covariance of the psychological and endocrine drug responses indicates that both are mediated by the same transmitter, likely norepinephrine in the case of amphetamine (42) and serotonin in the case of LSD. It is unlikely that glucocorticoids critically mediate the psychotropic drug response because the subjective effects of methamphetamine (51) and cocaine (52) are unaltered when the drug-induced cortisol response is pharmacologically augmented or blocked. On the other hand, the psychotropic effects of LSD might have contributed to the endocrine stress response. In fact, the subjective effects occurred faster than the cortisol response to LSD. However, only the subjective “good drug effects” and “stimulation” induced by LSD and not the “bad drug effects” or “fear” correlated with the steroid response over time. Thus, the endocrine changes in response to LSD seem be related to the positive and stimulant subjective LSD effects but not to anxiety.

Both cortisol and prolactin levels increase when the serotonin system is pharmacologically activated (35, 36, 53). Interestingly, the prolactin response was greater

after MDMA administration (33) than after LSD administration (3), whereas the glucocorticoid response was less, indicating differential effects of LSD and MDMA on markers of serotonergic activity and further supporting the view that the LSD-induced increase in glucocorticoids may have been enhanced by the more pronounced subjective effects of LSD.

A striking difference was found between the plasma concentration-effect curves of LSD in the present study and the plasma concentration-effect curves of MDMA in our previous study (33). Specifically, the plasma concentration-effect curve of MDMA showed pronounced clockwise hysteresis for the psychotropic effects of MDMA (33) and also for the cortisol and corticosterone responses (Supplemental Fig. S1A-C), suggesting acute tolerance to the effects of MDMA. In contrast, we observed no tolerance to the effects of LSD. This means that the effects of LSD on the HPA axis are longer-lasting than those of MDMA, although MDMA has a longer plasma half-life than LSD (31, 33). The finding could be explained by the pharmacological mechanisms of MDMA and LSD. MDMA releases endogenous serotonin and norepinephrine from presynaptic terminals (48), whereas LSD directly interacts with postsynaptic 5-HT receptors (2). In fact, the MDMA-induced cortisol response was blocked after duloxetine pretreatment, which prevents MDMA from interacting with the serotonin and norepinephrine transporters (47). In the case of cocaine, cocaine-induced euphoria is also short-lasting and exhibits acute tolerance (12), similar to MDMA, whereas the cortisol concentration-time curve is concordant with the cocaine-plasma concentration time curve (12), similar to LSD.

Unlike LSD, MDMA also increased the mineralocorticoids 11-deoxycorticosterone and aldosterone. Mineralocorticoids promote sodium retention and increase extracellular fluid volume, thereby increasing blood pressure (25). The MDMA-induced increase in mineralocorticoids may thus contribute to the greater increase in blood pressure after MDMA administration (33) compared with LSD (3). The mechanisms that underlie the differential effects of MDMA and LSD on mineralocorticoid production remain unclear.

LSD increased DHEA. DHEA is a precursor of many other steroids and may itself

modulate γ-aminobutyric acid-ergic and glutamatergic neurotransmission (54). DHEA has well-documented anxiolytic and antidepressant effects (54-57). An interesting line of investigation would be to further evaluate the role of DHEA in the potential anxiolytic effects of LSD that are reported in terminally ill patients (4).

The present study has limitations. First, only a single dose and single administration of LSD were used. However, a relatively high dose of LSD was administered, which produced pronounced psychotropic effects and was within the range of doses used clinically (4) and recreationally (1, 2). Additionally, we present LSD exposure-effect relationships that can partially substitute for a multiple dose-level study. Second, only psychiatrically and somatically healthy subjects with limited previous experience with hallucinogenic drugs were included. LSD may differentially affect steroid profiles in chronic LSD or polydrug users. Third, we did not assess concentrations of corticotropin-releasing factor or ACTH to describe the drug's effects on other mediators within the HPA axis.

In conclusion, LSD induced significant effects on plasma glucocorticoids, consistent with HPA axis stimulation via serotonergic receptors. Plasma levels of cortisol and particularly corticosterone covaried in close relation to the plasma levels of LSD over time. The corticosterone response was also closely related to the subjective effects of LSD. The glucocorticoid response to LSD showed no acute pharmacological tolerance, in contrast to the response to MDMA.

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DECLARATION: The authors of the manuscript have not conflicts of interest to declare.

Supplementary Data

Supplementary data associated with this article can be found in the online version.

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FIGURE LEGENDS

Figure 1. Plasma concentration-time profiles of glucocorticoids and mineralocorticoids following LSD or placebo administration. The values, obtained from 16 subjects, are expressed as mean ± SEM. LSD or placebo was administered at t = 0 h. LSD significantly increased the plasma concentrations of the glucocorticoids cortisol (B), cortisone (C), corticosterone (D), and 11-dehydrocorticosterone (E) compared with placebo. LSD did not alter plasma concentrations of the cortisol precursor 11-deoxycortisol (A) or the mineralocorticoids 11-deoxycorticosterone (F) and aldosterone (G). 11β-HSD, 11β-hydroxysteroid dehydrogenase; CYP, cytochrome P450. $*P < 0.05$, $**P < 0.01$, and $***P < 0.001$, compared with the time-matched placebo concentration (Tukey tests based on significant drug × time interactions in the two-way ANOVAs.

Figure 2. Plasma concentration-time profiles of androgens and progestogens following LSD or placebo administration. The values, obtained from 16 subjects (eight per sex for testosterone), are expressed as mean ± SEM. LSD or placebo was administered at t = 0 h. LSD significantly increased plasma concentrations of dehydroepiandrosterone (DHEA) compared with placebo (A). LSD also increased the area under the concentration-time curve but not the maximal concentration of androstenedione compared with placebo (C). In contrast, LSD did not alter plasma concentrations of dehydroepiandrosterone sulfate (DHEAS) (B) or testosterone (D, F). Similarly, LSD did not change plasma levels of the progestogens progesterone (G) and 17α-hydroxyprogesterone (E). 17β-HSD, 17β-hydroxysteroid dehydrogenase; CYP, cytochrome P450. $*P < 0.05$ and $***P < 0.001$, compared with the time-matched placebo concentration (Tukey tests based on significant drug × time interactions in the two-way ANOVAs.

Figure 3. LSD exposure-response relationships. LSD responses are shown as LSD effect (item "any subjective drug effect" reflecting the overall subjective response to LSD, cortisol or corticosterone concentration) minus the individual time-matched effect of placebo. Any subjective responses to LSD (A) and LSD-induced changes in cortisol (C) and corticosterone (E) over time are presented with the corresponding LSD concentrations over time (mean ± SEM) in 16 subjects. LSD or placebo was administered at t = 0 h. Subjective responses to LSD (B) and LSD-induced changes in cortisol (D) and corticosterone (F) concentrations (mean ± SEM) are plotted as a function of mean LSD plasma concentrations (hysteresis curves). The time of sampling is noted next to each point (in hours after LSD administration). The maximum concentration of LSD was reached 1.7 ± 1 h after LSD administration (A, B). The peak psychotropic effect was reached at 2.4 ± 0.8 h, with significant alterations in mental state from 0.5 h to > 10 h after LSD administration (A, B) (drug × time interaction in the two-way ANOVA: $F_{11,165} = 41.39$; $P < 0.001$). Maximum concentrations of cortisol (C, D) and corticosterone (E, F) were reached at 2.5 ± 0.8 h and 1.9 ± 0.5 h (mean ± SD), with significant elevations from 1.5 to 6 h and from 1 to 3 h after LSD administration, respectively

($F_{11,165}$ = 17.71; P<0.01 and $F_{11,165}$ = 13.35, P < 0.001, respectively). Counterclockwise hysteresis was observed for any drug effects (B) and cortisol (D), consistent with an initial delay between plasma concentration and effect that was attributable to drug absorption. Beyond 2 h after LSD administration, the psychotropic effects (A) and changes in plasma cortisol levels (C) decreased slowly, in parallel with the plasma levels of LSD, exhibiting a close concentration-effect relationship up to 24 h (B, D). LSD significantly increased plasma levels of cortisol 1.5-6 h after LSD administration (C). In contrast, plasma levels of corticosterone increased more rapidly but fell more quickly back to baseline levels, resulting in significant differences in plasma levels 1-3 h after LSD administration and compared with placebo (E). There was no evidence of acute pharmacological tolerance (clockwise hysteresis) for any of the effects of LSD. After drug administration, subjective drug effects increased together with plasma levels of corticosterone but more rapidly than plasma levels of cortisol (G, H). $*P < 0.05$ and $***P < 0.001$, compared with the time-matched placebo concentration (Tukey tests based on significant drug × time interactions in the two-way ANOVAs.

Table 1. Plasma steroid concentrations following LSD or placebo adminstration.

	C_{max}				AUC_{10}			
	Placebo	LSD	$^aF_{1,15}$	P value	Placebo	LSD	$^aF_{1,15}$	P value
Glucocorticoids								
Cortisol, nM	691±77	1060±40	19.78	<0.001	3545±247	6160±256	45.85	<0.001
Cortisone, nM	58.3±4.2	73.1±4.9	6.17	<0.05	349±23	507±31	25.05	<0.001
Corticosterone, nM	7.43±1.0	38.2±3.6	57.60	<0.001	27.9±2.2	101±9.8	48.66	<0.001
11-Dehydrocorticosterone, nM	4.43±0.7	8.70±0.7	13.97	<0.01	25.7±3.4	39.8±4.4	4.16	NS
Cortisol + Cortisone	737±81	1119±41	18.96	<0.001	3886±260	6666±267	45.86	<0.001
Cortisol/Cortisone ratio	13.9±1.1	20.1±1.3	32.76	<0.001	99.4±7.4	120±7.7	10.89	<0.01
11-Deoxycortisol *(precursor of cortisol)*, nM	1.67±0.3	2.53±0.5	2.09	NS	13.0±2.0	13.0±3.1	0.00	NS
Corticosterone + 11-Dehydrocorticosterone	11.7±1.6	46.4±4.2	46.00	<0.001	53.6±5.2	141±13.5	27.67	<0.001
Corticosterone/11-Dehydrocorticosterone ratio	2.26±0.3	5.13±0.4	34.11	<0.001	13.4±2.3	21.2±1.5	7.47	<0.05
Mineralocorticoids								
Aldosterone, nM	0.42±0.03	0.41±0.04	0.08	NS	3.33±0.1	3.33±0.13	0.00	NS
11-Deoxycorticosterone, nM	0.93±0.16	1.16±0.17	0.50	NS	7.03±1.5	9.94±1.7	0.99	NS
Androgens								
DHEA, nM	11.1±1.3	19.1±2.3	12.12	<0.01	71.9±6.8	106±12.1	10.33	<0.01
DHEAS, nM	1761±234	2070±318	1.03	NS	11551±1751	15224±2509	1.94	NS
Androsterone, nM	4.03±0.3	3.59±0.2	1.53	NS	26.3±1.1	27.0±0.9	0.23	NS
Androstendione, nM	3.68±0.5	4.37±0.5	2.03	NS	22.5±2.2	28.8±3.0	8.59	<0.01
Testosterone, nM	10.2±2.3	9.15±2.1	0.80	NS	71.8±17.1	71.3±15.8	0.54	NS
Testosterone in women, nM	2.07±0.4	1.58±0.3	1.30	NS	11.2±1.7	11.9±3.4	0.10	NS
Testosterone in men, nM	18.3±1.9	16.7±1.6	0.44	NS	132.4±14.1	123.3±9.9	0.65	NS
Testosterone/Androstendione ratio	4.50±1.0	3.85±0.9	3.62	NS	31.7±7.1	24.7±5.7	9.43	<0.01
5α-Dihydrotestosterone, nM	1.86±0.3	2.12±0.5	2.40	NS	8.55±1.8	8.03±1.6	0.04	NS
Progestins								
Progesterone, nM	0.22±0.03	0.31±0.05	2.05	NS	1.28±0.1	1.40±0.1	0.36	NS
17α-Hydroxyprogesterone, nM	2.99±0.5	2.96±0.4	0.00	NS	16.8±3.4	15.6±2.6	0.17	NS

Values are mean±SEM in 16 subjects. DHEA, dehydroepiandrosterone; DHEAS, dehydroepiandrosterone sulfate; C_{max}, peak plasma concentration; AUC_{10}, area under the concentration-time curve up to 10 h. NS, not significant. $^aF_{1,7}$ if only men or women.