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Altering Cortisol Level does not Change the Pleasurable Effects of Methamphetamine in Humans

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Preclinical studies have linked corticosteroid secretion and levels with drug self-administration by animals. In a double-blind, cross-over study, subjective, physiological, and endocrine responses to intravenous doses of methamphetamine 0.5 mg/kg or placebo were assessed in eight methamphetamine-experienced subjects after three cortisol-modifying premedication conditions: augmenting cortisol level with oral hydrocortisone 50 mg, blocking cortisol response with the corticosteroid synthesis inhibitor metyrapone 1500 mg orally, or no premedication. Although the pharmacologic manipulations produced the expected hormonal changes, subjective response to the methamphetamine showed few differences. Diminishing cortisol response by pharmacologic blockade did not alter the pleasurable effects of methamphetamine. Hydrocortisone did increase self-reported 'bad drug effect' and decreased craving after saline placebo relative to the period following methamphetamine. Metyrapone was associated with significant premature ventricular complexes in two subjects during methamphetamine administration and may not be safe for those who use methamphetamine.
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INTRODUCTION

Addiction can be viewed as a dysregulation of brain reward systems resulting in compulsive use and loss of control over drug taking (Koob and Le Moal, 2001). Therefore, pharmacological treatments for drug dependence have targeted decreasing the rewarding effects of the drug or decreasing response to triggers for drug use, such as stress or environmental cues. Studies in rodents have linked corticosteroid secretion and levels with animal models of addiction in each of these areas (reviewed in Goeders, 2002). Much of this investigation has been carried out with stimulant drugs, such as cocaine or amphetamines. Surgical and chemical adrenalectomy decreases ongoing cocaine self-administration (Goeders, 1997; Goeders and Guerin, 1996) and relapse to drug self-administration (Piazza *et al*, 1994) in rodents. A decrease in drug self-administration after lowering corticosteroid levels may be due to a decrease in the rewarding effects of the drug, reducing it below a threshold for continued use. ACTH (Jouhaneau-Bowers and Le Magnen, 1979) and corticosterone (Deroche *et al*, 1993) have been reported to maintain their own self-administration in rats, suggesting that these hormones themselves can function as positive reinforcers (Goeders, 1997). The effects of cortisol on the rewarding effects of drugs in humans have been relatively less examined, particularly methamphetamine, the most widely used, illegally manufactured and distributed stimulant drug in the world (CDC, 1995).

This study evaluated the consequences of raising cortisol levels with hydrocortisone or blocking cortisol response with the cortisol synthesis inhibitor, metyrapone, on the subjective effects of intravenous (i.v.) methamphetamine in humans. We chose metyrapone as the cortisol synthesis inhibitor because it does not have the mild glucocorticoid receptor inhibitory effects of another commonly used agent, ketoconazole (Loose *et al*, 1983), which could confound the interpretation. Metyrapone also does not block dehydroepiandrosterone (DHEA) response (as does ketoconazole), which may play a role in the subjective response to stimulant or stimulant-like drugs of abuse (Harris *et al*, 2002), possibly through its actions on serotonin and affect (Majewska, 1995).

METHODS

Subjects

Subjects were recruited by newspaper ad and word of mouth (subject referral). Inclusion criteria were age 21–45

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years, self-reported i.v. methamphetamine use at least six times and at least once in the past year, and body weight within 15% of ideal weight according to life insurance tables. We recruited methamphetamine-experienced subjects because they would likely be closer in response to methamphetamine-dependent patients than normal volunteers, yet more likely than dependent subjects to complete the experiment. Exclusion criteria were significant medical (including psychiatric and endocrine) illness, pregnancy, treatment of substance abuse in the last 12 months, current dependence on any drug except nicotine or caffeine, the use of steroid (including topical) medication in the last 3 months, the use of other medications which might impair the ability to safely complete the study or alter drug kinetics, or sensitivity to any of the experimental medications.

Subjects gave informed consent and were paid for their participation. The study was approved by the Committee on Human Research (IRB), University of California, San Francisco (UCSF).

The study began with 12 subjects. Two dropped out for personal reasons. Two were terminated prior to completion because of frequent premature ventricular complexes (PVCs). Data from dropouts and terminated subjects are not reported except as noted. Eight men completed the study. The study was terminated after eight subjects because the only manufacturer ceased production of metyrapone and we were unable to obtain further supplies. One subject was self-identified as Hispanic, three as non-Hispanic white, one as Native-American, and three as being of mixed ethnicity. The mean age was 34 years (range, 25–44 years). None were HIV positive. The preferred drug administration route was i.v. for four subjects, inhalation for three, and smoking for one, but all had previous i.v. experience. Subjects reported using on average what they believed was 1/8 to 1/2 g of methamphetamine per occasion.

Materials

Dextromethamphetamine was obtained from Sigma Chemical Corp. (St Louis, MO) and recrystallized. Purity and identity were determined by gas chromatography-mass spectrometry (GC-MS), high-performance liquid chromatography (HPLC), and thin layer chromatography (TLC). The enantiomeric purity was determined by derivatizing the compounds with trifluoroacetylimidazole and analyzing the trifluoroacetyl amides by GC-MS on a Restek chiral beta-DEXcst column, employing the Restek temperature program for separation of the methamphetamine enantiomers. The i.v. solution of 0.5 mg/kg was prepared under sterile conditions as a Millipore filtered 1% stock solution in sterile 0.9% sodium chloride. The administered dose units were diluted to 10 ml volume for injection. Metyrapone capsules were obtained from Novartis Pharmaceuticals Corporation (East Hanover, NJ). Hydrocortisone capsules were prepared by crushing tablets obtained from West-Ward Pharmaceutical Corporation (Eatontown, NJ). Placebo capsules contained lactose monohydrate (USP/NF).

Procedures

After screening, including routine admission laboratory tests, EKG, and physical examination, subjects were admitted to the General Clinical Research Center (GCRC) at UCSF. Subjects were asked to abstain from drug and alcohol use, except for nicotine and caffeine, for 48 h prior to admission. On admission, subjects provided a urine sample for urine toxicology screen and urinalysis and a blood sample for general admission laboratory screening tests. The study session was postponed if evidence of acute illness or recent illicit drug use was present.

Subjects refrained from caffeine and nicotine use after midnight of the day prior to testing. On the morning of the drug administration day, subjects ate a standardized breakfast. Testing began at approximately the same time each morning for each session to minimize circadian differences. Three premedication conditions of metyrapone, hydrocortisone, or placebo preceded methamphetamine or placebo administration for a total of six treatment conditions. In the metyrapone condition, 750 mg of the drug was given orally, followed 3.5 h later by another 750 mg, followed 30 min later by methamphetamine or placebo. This dosing regimen, based on that of Young *et al* (1995), was intended to produce a significant decrease in cortisol levels. In the hydrocortisone condition, 50 mg of hydrocortisone was given orally and was followed 1.5 h later by methamphetamine or placebo (Derendorf *et al*, 1991). In each of the three premedication conditions (metyrapone, hydrocortisone, or placebo), placebos were substituted for the other drug(s). All oral drugs were administered in identical gelatin capsules. Methamphetamine 0.5 mg/kg or normal saline placebo was injected into a forearm vein at a constant rate over 10 min by infusion pump. Measures were obtained over the next 48 h at which time the subject was discharged.

For convenience, the six conditions are designated as follows:

Met/MA	metyrapone and methamphetamine infusion
Met/S	metyrapone and saline infusion
HC/MA	hydrocortisone and methamphetamine infusion
HC/S	hydrocortisone and saline infusion
P/MA	placebo capsules and methamphetamine infusion
P/S	placebo capsules and saline infusion

Measures

Blood samples were obtained from a venous catheter in the subject's opposite forearm in order to collect samples for assay of plasma methamphetamine and amphetamine, corticotropin (ACTH), cortisol, deoxy cortisol and DHEA concentrations. All samples were immediately placed on ice. Plasma was separated by spinning in a refrigerated centrifuge within 30 min of collection and stored at $-70^{\circ}C$ until assay.

All urine was collected and urine pH measured from admission until drug administration and from 0–24 h after methamphetamine dosing for assay of free urinary cortisol and 11-deoxycortisol.

Samples for assay of plasma methamphetamine and its major psychoactive metabolite amphetamine (Cho and Kumagai, 1994) were obtained prior to beginning the infusion and at 10 and 30 min and 1, 2, 4, 6, 8, 18, 24, and

48 h afterwards. Methamphetamine and amphetamine were quantified by procedures based on published methods using GC (Jacob *et al*, 1995).

Quantitative determinations of plasma cortisol, DHEA, and ACTH concentrations were made using enzyme-linked immunosorbent assay (EIA) kits (cortisol and DHEA kits from Diagnostic Systems Laboratories, Webster, TX, and ACTH kits from ALPCO Diagnostics, Windham, NH). Plasma and urinary 11-deoxycortisol levels were quantified by HPLC (Kater *et al*, 1992). At the times plasma deoxycortisol levels were assayed, plasma cortisol level was also determined by this method. This HPLC-determined cortisol level was included in the cortisol–plasma–time concentration curves, because the two methods (HPLC and EIA) produced comparable results ($r = 0.999$). Plasma samples for the assay of cortisol levels were drawn twice before metyrapone/placebo dosing, twice before methamphetamine/saline infusion, and at 15, 30, and 45 min and 1, 1.5, 2, 3, 4, 6, 24, and 48 h after starting the infusion. Plasma was collected for ACTH assay at the same times as for cortisol before the infusion and at 5, 10, 15, 20, 30, 45 min and 1, 1.5, 2, 6, 24, and 48 h afterwards. Plasma for DHEA measurement was collected once prior to metyrapone/placebo dosing, once prior to the infusion, and at 1 and 2 h after the infusion. Plasma for 11-deoxycortisol was collected for measurement once before metyrapone/placebo dosing, once prior to the infusion, and at 10 min after the start of the infusion (ie immediately after). Urine-free cortisol and deoxycortisol were collected for assay during the 24 h after methamphetamine or placebo dosing and compared between conditions.

Vital signs were recorded after the subject was recumbent for at least 5 min. Heart rate and blood pressure were monitored using a physiological patient monitor (Escort II+, Model 20301, Medical Data Electronics, Inc., Arleta, CA). Skin and tympanic (core) temperatures were measured using thermocouples on an index finger and adjacent to the tympanic membrane (Mallinkrodt Mon-a-therm Model 6500, Mallinkrodt Medical, Inc., St Louis, MO). The respiratory rate was obtained by counting respirations. Vital signs were obtained immediately before each drug or placebo administration and every 30 min from the first metyrapone/placebo administration until MA/P administration, then frequently during the infusion until 30 post (for safety reasons), and at 45 min and 1, 1.5, 2, 3, 4, 6, 8, 18, 24, 30, 42, and 48 h after beginning the infusion. For statistical comparison, the following time points were used: immediately preinfusion and 5, 10, 15, 20, 25, 30, and 45 min and 1, 1.5, 2, 3, 6 h afterwards.

Subjects were asked how intoxicated they were on a scale of 0–100 with 0 being 'not intoxicated' and 100 being 'the most intoxicated you have ever been' after methamphetamine. This measure was obtained immediately before each drug or placebo administration, then at 5, 10, 15, 30, and 45 min, and 1, 1.25, 1.5, 1.75, 2, 3, 4, 6, 8, 12, 24, and 48 h postinfusion. Visual analog scales (VAS) measured other subjective effects, 'High,' 'Any Drug Effect,' 'Good Drug Effect,' 'Bad Drug Effect,' 'Euphoria,' and 'Drug Liking' on a 100 mm line from 0 ('none') to 100 ('most ever') and craving measures, 'Desire to Use' and 'Likely to Use,' from 0 ('not at all') to 100 ('extremely') with 'mildly' and 'moderately' indicated above the line between the two extremes (Berger *et al*, 1996). These were obtained at baseline and at 15 and 30 min and 1, 1.5, 2, 3, 4, 6, 8, 24, and 48 h postinfusion.

We also assessed mood changes using the Profile of Mood States (POMS) (McNair *et al*, 1971), a 65-item checklist used to assess subjective mood changes: tension-anxiety, depression-dejection, anger-hostility, vigor, confusion, and fatigue. Subjects rated the presence and intensity of symptoms on a 0–4 scale with zero as 'no effect' and 4 as 'extremely strong.' We chose the VAS as our primary dependent variables in preference to the more general subjective mood states measured by the POMS because the VAS measure symptoms specific to our hypotheses (ie rewarding effects, such as 'Drug Liking' and 'High').

Data Analysis

Mean physiologic, hormonal, and subjective data were compared among experimental conditions by repeated measures analysis of variance (ANOVA) models. Drug condition and observation time were considered within-subject factors. Change from preinfusion value was used in the analyses, except for the plasma hormonal concentrations and the analysis of the values immediately pre-methamphetamine/saline infusion. The majority of predetermined data points (>98%) were collected as planned. For each missing data point, the average of the values immediately before and after for that subject was substituted. If the F-test was significant, pairwise comparisons were performed using the least squares means analysis. Correlations between variables were obtained using the nonparametric test Kendall's tau, because of the small sample size and distribution of data. Within-subject comparisons between time points were calculated using the Wilcoxon Matched Pairs Signed Ranked Test. Effects were considered statistically significant at $p < 0.05$. One subject refused to use our definition of Euphoria, attributing to it a more spiritual meaning, in conflict with a definition of an effect by any drug. His Euphoria ratings were removed from analysis.

RESULTS

Hormonal Changes

Cortisol. Metyrapone and hydrocortisone produced the expected changes in plasma cortisol levels. Plasma cortisol was significantly different between conditions ($p = 0.0001$): HC/MA, HC/S > P/MA > P/S, Met/MA, Met/S (Figure 1). Hydrocortisone 50 mg increased plasma cortisol level from a mean ($\pm$ SD) of 7.7 ± 3.8 and 8.6 ± 2.3 mcg/dl at morning baseline to 41.4 ± 8.9 and 39.6 ± 14.3 mcg/dl just prior to methamphetamine/saline administration in the HC/MA and HC/S conditions, respectively. Methamphetamine alone significantly increased ($p < 0.02$) the mean cortisol level from 8.7 ± 2.4 mcg/dl just prior to administration to 23.2 ± 22.6 at a mean peak level 45 min after dosing. Metyrapone 1500 mg suppressed this rise in cortisol following methamphetamine dosing. Cortisol significantly decreased from a baseline of 7.6 ± 1.9 to 5.9 ± 1.7 in the Met/MA condition ($p < 0.03$), but did not decrease significantly in the Met/S condition (6.7 ± 2.3 to 6.0 ± 1.8, NS). The decrease in cortisol in the Met/MA is consistent

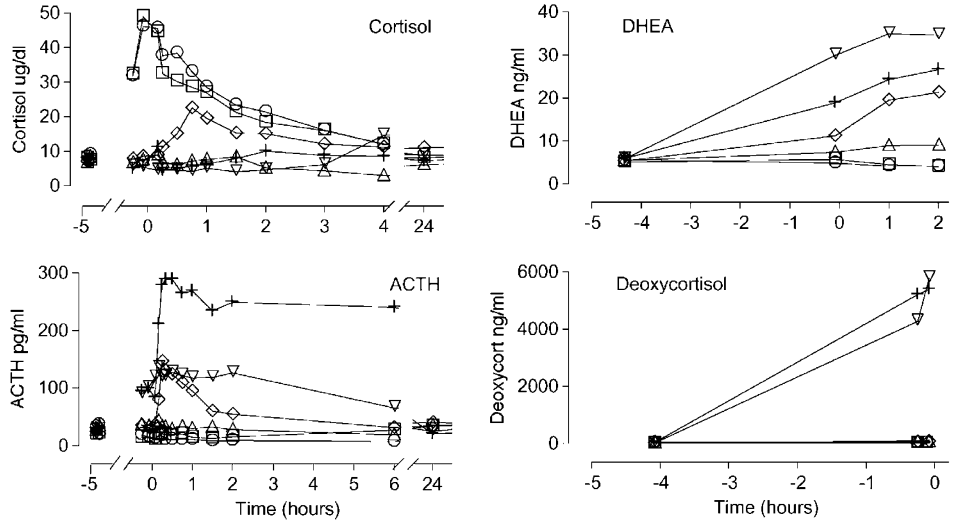

Figure 1 Plasma hormonal responses in the six study conditions: + —Met/MA; ▽ —Met/S; □ —HC/MA; ○ —HC/S; ◇ —P/MA; △ —P/S.

with a circadian decrease during this time period. Urinary free cortisol concentration collected for 24 h after methamphetamine dose was significantly different between conditions ($p = 0.0001$): HC/MA, HC/S > P/MA, P/S, Met/MA, Met/S.

ACTH. This also differed between conditions ($p = 0.0001$): Met/MA > Met/S, P/MA > P/S, HC/MA, HC/S (Figure 1). Metyrapone 1500 mg increased mean plasma ACTH level from morning baseline to just prior to methamphetamine/saline administration in the Met/MA and Met/S conditions. Methamphetamine further increased ACTH in the Met/MA condition. Methamphetamine alone increased ACTH from just prior to dosing to mean peak 15 min afterwards. Hydrocortisone suppressed this rise in response to methamphetamine in the HC/MA condition.

DHEA. Plasma DHEA showed a pattern similar to ACTH (Figure 1). However, the difference between conditions did not reach significance.

Deoxycortisol. Plasma deoxycortisol was significantly different between conditions ($p = 0.0001$): Met/MA, Met/S > P/MA, P/S, HC/MA, HC/S (Figure 1). Metyrapone increased mean plasma 11-deoxycortisol over 100 fold. Plasma deoxycortisol did not change in the other four conditions. Urinary deoxycortisol was also significantly different between conditions ($p = 0.0001$): Met/MA > Met/S > P/MA, P/S, HC/MA, HC/S.

Physiological Measures

Mean changes in systolic and diastolic blood pressure, heart rate, and rate–pressure product were significantly elevated in the first 6 h after methamphetamine dosing in all active methamphetamine conditions compared to all saline conditions (Figure 2). Mean changes in systolic blood pressure, heart rate, and rate–pressure product in the Met/MA condition were significantly lower across time than in the HC/MA condition. The mean peak rate–pressure product change was also significantly lower in the Met/MA condition. The mean diastolic blood pressure across time, on the other hand, was significantly increased in the methamphetamine-alone condition compared to the HC/MA condition and showed a trend toward significance ($p < 0.08$) compared to the Met/MA condition. The mean respiration rate was significantly elevated in the HC/MA condition across time compared to all other conditions (using active methamphetamine or placebo), as was peak change. However, these differences in changes in heart rate, blood pressure, and respiration rate between methamphetamine conditions may have been due to slightly higher or lower premethamphetamine values for the conditions, as raw score ANOVAs were not significantly different.

Subjective Symptom Measures

Subjective effects (Figure 3) peaked 15 min after the start of methamphetamine dosing. Mean $\pm$ SD (range) peak intoxication in the methamphetamine-alone condition was 45 ± 23 (20–95). Subjects reported a level of intoxication within the range of what they typically experienced during methamphetamine use outside the laboratory (even though reported quantities with outside use were typically higher). The mean peak Bad Drug Effect was significantly higher in the HC/MA condition than in all other conditions. The mean Bad Drug Effect across time was also higher in the HC/MA condition than the Met/MA condition across time, but did not reach significance compared to that in the methamphetamine-alone condition. The only differences in Desire to Use methamphetamine or Likely to Use methamphetamine were that the Mean Desire to Use and Likely to Use across time and mean peak change in Likely to Use ratings were lower in the HC/S condition compared to the HC/MA condition. The other VAS subjective drug effects (Any Drug Effect, Drug Liking, Euphoria, Good Drug Effect, High, or Intoxication) did not differ between methamphetamine conditions. Two subjects rated Drug Liking considerably lower than the others in the methamphetamine-alone condition (peak values of 20–21 out of 100 compared

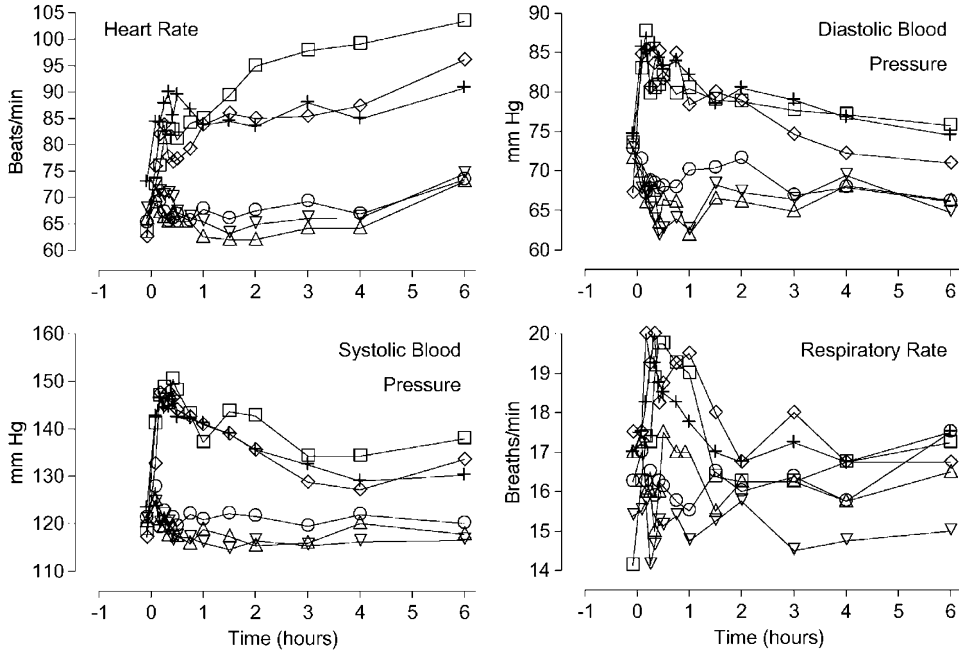

Figure 2 Physiological responses in the six study conditions (symbols as described above).

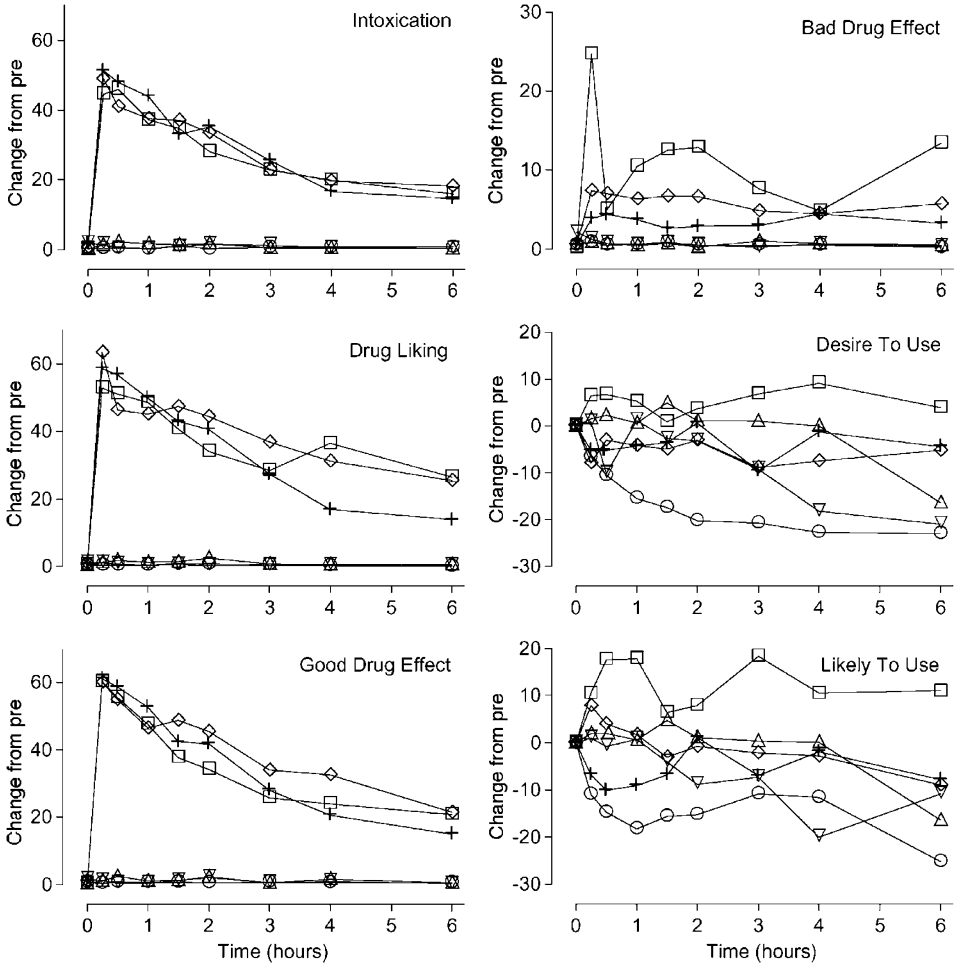

Figure 3 Subjective responses in the six study conditions (symbols as described above).

to the rest of the subjects with peaks of 54–91). In these subjects, cortisol increased Drug Liking and metyrapone decreased it. POMS scores were not significantly different between conditions, except for the tension-anxiety scale and the vigor scale. In general, self-ratings of these two scales were higher with methamphetamine than with saline, although only some *post hoc* comparisons were significant. There were no significant differences between methamphetamine conditions.

Methamphetamine Kinetics

Plasma methamphetamine concentrations did not differ between methamphetamine conditions. Mean peak methamphetamine concentrations ($\pm$ SD) were 92.8 ($\pm$ 25.2) ng/ml, 96.7 ($\pm$ 45.9) ng/ml, and 110 ($\pm$ 83.9) ng/ml for the HC/MA, P/MA, and Met/MA conditions, respectively. Most plasma amphetamine levels were below the level of detection, so differences between conditions were not analyzed.

Hormone-Subjective Effects Relations

The correlations between plasma cortisol, DHEA, and ACTH levels and subjective effects were examined in the methamphetamine-alone condition in order to assess the relations between changes in these hormone levels following methamphetamine administration and subjective effects. The mean ACTH peaked at the same time as most subjective measures (see Figures 1 and 3). However, rise in ACTH was not correlated with subjective symptom ratings. Cortisol and DHEA levels peaked later, cortisol at 45 min after dosing and DHEA at 1–2 h. Although positively correlated with pleasurable drug effects in general, cortisol levels were not significantly correlated with pleasurable drug effects at its peak time. The cortisol level was significantly correlated with drug effect ratings at *earlier* times. The rise in cortisol at 1 h after dosing (but not 45 min post) was significantly positively correlated with Any Drug Effect at 15 and 30 min ($p < 0.02$, $p < 0.05$, respectively), Good Drug Effect at 15 min ($p < 0.05$), High at 15 min ($p < 0.04$), and a trend with Euphoria at 15 and 30 min (both $p < 0.06$). The rise in DHEA level at 1 h was significantly positively correlated with Good Drug Effect at 30 min ($p < 0.03$) with a trend at 1 h ($p < 0.09$) and significantly negatively correlated with Bad Drug Effect at 1 h ($p < 0.05$) with a trend at 15 and 30 min ($p < 0.08$ and $p < 0.07$, respectively).

Adverse Effects

In the Met/MA condition, two subjects developed frequent unifocal PVCs (not torsades de pointes) about 9 min into the 10 min methamphetamine infusion. The PVCs resolved over the next half hour without treatment. Physiological and hormonal effects and plasma methamphetamine levels in these subjects were not unusual compared to the others with the following exceptions. One subject had a plasma peak ACTH level in the Met/MA condition over three SDs above the mean of eight who completed the study. The other subject with PVCs had a plasma peak DHEA level almost four SDs above the mean of the eight completers. Deoxycortisol levels in the two subjects with PVCs were not unusual compared to those of the rest of the subjects.

DISCUSSION

Despite expected hormonal changes, raising cortisol level or blunting cortisol response did not produce significant mean changes in most subjective effects of methamphetamine. Metyrapone administration kept cortisol concentrations almost below dexamethasone suppression levels (< 5 mcg/dl). In other studies, attenuation of the HPA axis response did not change cocaine-seeking behavior in Rhesus monkeys (Broadbear *et al*, 1999) or subjective effects in humans (Ward *et al*, 1998, 1999), nor did administration of a larger dose of hydrocortisone (100 mg) to normal volunteers affect the subjective response to a relatively lower dose of another amphetamine, oral D-amphetamine 20 mg (Wachtel *et al*, 2001). A social stress test increasing cortisol levels *decreased* the initial subjective response to a lower oral dose of D-methamphetamine (10 mg) in normal volunteers (Soderpalm and deWit, 2001).

The two subjects in our study with the lowest Drug Liking reports in the methamphetamine-alone condition showed the expected changes; that is, hydrocortisone increased Drug Liking and metyrapone decreased it. The response of these two subjects may be comparable to that in studies of animals receiving lower doses of stimulants. Once some stimulant dose threshold is reached, blunting corticosteroid response may no longer blunt the rewarding effect (Goeders, 2002); that is, it may not be possible to decrease the rewarding effect of a higher dose of stimulant by blunting cortisol response. Increasing corticosteroid levels may even push individuals to the descending limb of an inverted U-shaped 'HPA function' response curve (Kosten and Ambrosio, 2002), producing a decrease in rewarding effect similar to the decrease in behavioral response in animals seen in some studies (reviewed in Kosten and Ambrosio, 2002).

A limitation of our study is that only one dose of methamphetamine was used. A lower dose may have produced the expected changes in more of the subjects. The study by Wachtel *et al* (2001) with its lower relative amphetamine dose (20 mg PO) may have been more likely to produce the expected results, but it also reported no enhanced pleasurable effects. However, the amphetamine dose used may still have not been low enough. Alternatively, the hydrocortisone dose (100 mg) in that study may have been too high. Soderpalm and deWit (2001), using a stress test which produces a smaller increase in cortisol using moderate psychological stress (Kirschbaum *et al*, 1993; Kudielka *et al*, 1998), found a *decreased* initial subjective response to a lower dose (10 mg) of oral methamphetamine; but perhaps that sample of predominantly stimulant-inexperienced volunteers was more sensitive to lower doses, so that the methamphetamine doses were still above the threshold for enhancement of rewarding effects by increased cortisol concentration.

In any case, persons taking a cortisol-lowering agent for treatment for methamphetamine dependence would likely be using a methamphetamine dose above the threshold for a rewarding effect even without any corticosteroid augmenta-

tion or would quickly discover that an increased dose would restore the rewarding effects if the medication did decrease it. The increase in cocaine use in methadone-maintained patients during a treatment trial of ketoconazole (Kosten *et al*, 2002) would be consistent with this prediction, although this interpretation is complicated by administration of hydrocortisone in that study.

Instead of increasing the pleasurable effects from methamphetamine, hydrocortisone increased ratings of Bad Drug Effect. This increase in unpleasant effects might also suggest that our sample is predominantly at the peak or on the descending limb of an inverted U-shaped methamphetamine response curve with cortisol levels beyond an optimal value and associated with a decreasing rewarding effect. Alternatively, genetic (Kosten and Ambrosio, 2002) or perhaps experiential (Maccari *et al*, 1991a, b) differences may make individuals such as those in our sample differentially sensitive to the effects of corticosteroids. Wachtel *et al* (2001) found that their higher dose of hydrocortisone produced dysphoric effects on its own which worsened with the addition of amphetamine.

In the methamphetamine-alone condition, a rise in plasma cortisol level was correlated with a rise in measures of rewarding effects of methamphetamine at earlier times. This is consistent with the similar effect curves of cortisol level and pleasurable effects after cocaine use (Mendelson *et al*, 2002). However, in the present study, subjective effects occurred before the changes in cortisol level, suggesting that they were not a result of the cortisol change, but both might be due to a common precipitant. DHEA level was negatively related to Bad Drug Effect at the same time point. In this case, causality cannot be ruled out based on timing. However, this raises the possibility that DHEA may counteract some of the unpleasant effects or, conversely, a lower intensity of unpleasant effects may lead to higher levels of DHEA. Experimental manipulation of DHEA level would be needed to test this.

The Desire to Use and the Likely to Use ratings were different after hydrocortisone depending on the methamphetamine condition (active or placebo). This divergence in craving measures appears similar to the divergence in drug seeking in rats after serotonin depletion. Serotonin depletion in rats decreased drug seeking during extinction, but enhanced drug seeking after cocaine-paired cues and priming (Tran-Nguyen *et al*, 2001). It may be relevant that corticosteroids modulate serotonin receptor activity, exerting inhibitory control of some serotonin receptors (Chaouloff, 1995), although other neurochemical mechanisms are also possible. Together, these findings suggest that some pharmacological interventions might increase or decrease the desire to use or intent to use stimulant drugs depending on the extent of environmental trigger exposure. An implication is that clinical trials might benefit from examining treatment response based on the extent of exposure to the drug.

Two subjects had frequent PVCs after methamphetamine in the metyrapone conditions. No PVCs occurred in the other conditions, although PVCs with a lesser frequency have occasionally occurred in our other methamphetamine studies (without metyrapone). One explanation of this possible interaction would be increased cardiac automaticity due to an accumulation of deoxycortisol, produced when metyrapone blocks the enzyme 11β-hydroxylase which converts deoxycortisol into cortisol (Goldfien, 1995) Some corticosteroids potentiate isoproterenol-induced cardiotoxicity. Prednisone and desoxycorticosterone acetate potentiate the arrhythmogenic property (ventricular fibrillation) of isoproterenol in rats (Guideri *et al*, 1978). Deoxycortisol may have arrhythmogenic properties similar to desoxycorticosterone acetate and may potentiate arrhythmogenicity from methamphetamine. However, deoxycortisol levels in our two subjects were not higher than levels of the subjects without PVCs, suggesting a difference in underlying cardiovascular functioning. Even if metyrapone were helpful for some highly motivated low-dose methamphetamine users, the possibility of cardiotoxic effects during a lapse in abstinence might pose a medical risk.

CONCLUSIONS

Neither raising cortisol level nor blunting cortisol response altered the pleasurable effects of methamphetamine. Replicating in humans findings from animal studies is important. Our negative findings may be the result of too high a methamphetamine dose; however, the dose seemed consistent with that self-administered by the experienced methamphetamine users. Hydrocortisone did increase unpleasant effects. Despite this, or perhaps because of this, hydrocortisone produced opposite effects on craving depending on whether subjects received methamphetamine or not. Metyrapone use may place some patients at increased risk of adverse cardiovascular effects when they use methamphetamine concurrently.

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