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Faculty of Psychology

Stress reactivity in heroin dependence

A cumulative dissertation

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by

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(Dean)

Acknowledgments

Declaration of independence

I declare, that the present dissertation is my self-contained work. I wrote the individual papers in collaboration with the mentioned co-authors. The articles were submitted and published by the named scientific journals only. All citations were indicated and solely the cited tools were used. All authors have agreed to the submission of the articles in this form, and there were no biomedical financial interests or potential conflicts of interest.

For the purpose of my cumulative dissertation, I present the following original and peer-reviewed articles. Their copies can be found in the appendix.

Article 1:

Gerber, H., Borgwardt, S. J., Schmid, O., Gerhard, U., Joechle, W., Riecher-Rössler, A., Wiesbeck, G. A., & Walter, M. (2012). The impact of diacetylmorphine on hypothalamic-pituitary-adrenal axis activity and heroin craving in heroin dependence. *European Addiction Research, 18*, 116–123. IF= 2.35

Article 2:

Walter, M., Gerber, H., Kuhl, H. C., Schmid, O., Joechle, W., Lanz, C., Brenneisen, R., Schächinger, H., Riecher-Rössler, A., Wiesbeck, G. A., & Borgwardt, S. J. (2013). Acute effects of intravenous heroin on the hypothalamic-pituitary-adrenal axis response. A controlled trial. *Journal of Clinical Psychopharmacology, 33,* 193–198. IF= 4.09

Article 3:

Blum, J., Gerber, H., Gerhard, U., Schmid, O., Petitjean, S., Riecher-Rössler, A., Wiesbeck, G. A., Borgwardt, S. J., & Walter, M. (2013). Acute effects of heroin on emotions in heroin-dependent patients. *American Journal on Addictions, 22,* 598–604. IF= 1.67

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Tables and figures

Abstract

Background: Heroin dependence is a chronic relapsing disorder characterized by a compulsion to seek and use heroin despite the negative consequences. In addition to the diagnostic criteria, heroin dependence is associated with an altered function of the hypothalamic-pituitary-adrenal (HPA) axis and with affective disturbances and other mental disorders. Stress and heroin craving are considered as key motivators for heroin use. Heroin-assisted treatment (HAT) is suitable for chronic heroin-dependent patients who do not benefit of other therapy forms.

Methods: The acute effects of intravenous diacetylmorphine (DAM, pharmaceutical heroin) on the HPA axis response and on the emotions in heroin-dependent patients compared with placebo and with healthy controls were examined. Twenty-eight heroin-dependent patients in stable HAT and twenty age and gender matched healthy controls were recruited for a randomized, controlled crossover trial. Patients were administered heroin (DAM) or placebo (saline), healthy controls received only saline. HPA axis response was measured by adrenocorticotropic hormone (ACTH) and by cortisol concentrations in plasma, serum and saliva to three time points (before, 20 and 60 minutes after the substance administration). Withdrawal syndrome, craving, mood, anxiety and anger were measured before and 60 minutes after the substance application using validated questionnaires. Plasma concentrations of heroin and its main metabolites were assessed using high-performance liquid chromatography.

Results: Compared to placebo, DAM administration reduced withdrawal, anxiety and anger in heroin-dependent patients and was associated with significant decreases in the ACTH and cortisol concentrations ($p < 0.01$). After placebo, all hormone levels were significantly higher in patients than in healthy controls ($p < 0.01$). When patients received DAM, their cortisol concentrations did not differ from healthy controls and their ACTH levels were significantly lower ($p < 0.01$). The concurrent cocaine use had no significant influence on the HPA axis response. Before substance injection, heroin-dependent patients showed significantly higher anxiety and depression scores than healthy controls ($p < 0.0001$). Irrespective of the patients' perceived intoxication and sedation, DAM administration was associated with a significant decrease in all negative emotions and in heroin craving, and with a significant increase in emotional well-being ($p < 0.0001$). When patients received DAM, they did not differ from healthy controls in their emotions at the end of the experiment.

Conclusion: Acute DAM administration suppresses the stress response, dampens craving and negative emotions and increases positive emotions in heroin-dependent patients in a stable opioid maintenance program (HAT). Patients showed normalized HPA axis responses and emotional states, when they received their regular DAM dose. These findings indicate that heroin (DAM) − considered as a stress-protective factor – contributes to the regulation of the stress sensitivity and emotional vulnerability in heroin-dependent patients, and thus underscore the clinical benefit of HAT for chronic heroin dependence.

1.   Theoretical background

1.1.   Heroin dependence and stress

Heroin dependence is a chronic relapsing brain disorder, characterized by compulsive heroin seeking and its use, despite the negative consequences (Leshner, 1997). The Diagnostic and Statistical Manual of Mental Disorders (DSM) and The International Statistical Classification of Diseases (ICD) describe substance abuse as a maladjusted pattern of substance use leading to significant impairment or distress, as manifested in users' physical and mental health and their social life (Dilling, Mombour, & Schmidt, 2000; Sass, Wittchen, Zaudig, & Houben, 2003). Moreover, substance dependence is characterized by *tolerance* (increased amounts of the substance to achieve the desired effect), *craving* (an overwhelming impulse to substance use), *loss of control* of substance use and *withdrawal symptoms* (aversive physical and psychical phenomena when substance use is disrupted). Typically, the users spend a lot of time with providing the substance, with using it and with recovering from its effects. The family and social life and the job-related functions are thereby neglected, and consequently they are often lost. Although the users know these negative consequences of the substance use, they cannot stop it.

In heroin-dependent patients, a considerable comorbidity with other psychiatric symptoms and impairments has been observed (Frei & Rehm, 2002; Walter & Gouzoulis-Mayfrank, 2014). Especially, the use of other substances (Stitzer & Sigmon, 2006), personality disorders (Hasin, Fenton, Skodol, Krueger, Keyes, Geier et al., 2011; Verhoul, 2001), affective disorders and anxiety (Merikangas, Mehta, Molnar, Walters, Swendsen, Aguilar-Gaziola et al., 1998) as well as subsequent physical damages (Fingerhood, 2006) have been found. Moreover, high criminality rates, infectious diseases, stigmatisation, social decline and homelessness are the consequence of chronic heroin dependence (Uchtenhagen, 2010). For substance use, a lifetime prevalence of 3% and 0.1–1.6% for heroin dependence is estimated (Crum, 2006; Kessler, Berglund, Demler, Jin, Merikangas, & Walters, 2005).

Stress – reaction of the organisms on perceived stress factors for the purpose to cope with special requirements of the environment (Lazarus & Folkman, 1884) – is closely associated with substance use (Brown, Wisniewski, & Dobs, 2006; Walter, Dammann, Wiesbeck, & Klapp, 2005). Stress has been shown to increase anxiety and the secretion of adrenocorticotropic hormone (ACTH) and cortisol (Grillon, Duncko, Coivington,

Kopperman, & Kling, 2007; Sinha, Talih, Malison, Cooney, Anderson, & Kreek, 2003). Furthermore, in heroin-dependent patients, stress factors, drug cues and negative mood are associated with elevated craving and relapse (Epstein, Willner-Reid, Vahabzadeh, Mezghanni, Lin, & Preston, 2009; Fox, Talih, Malison, Anderson, Kreek, & Sinha, 2005; Sinha, Garcia, Paliwal, Kreek, & Rounsaville, 2006).

The stress response as a function of the hypothalamic-pituitary-adrenal (HPA) axis is maladaptive in substance users. Whereas elevated stress hormone levels have been found in cocaine use (Broadbear, Winger, Cicero, & Woods, 1999), heroin − as well as other opiates (e.g. morphine) − is associated with a suppression of the stress hormone secretion (Walter, Wiesbeck, Bloch, Aeschbach, Olbrich, Seifritz et al., 2008; Walter, Wiesbeck, Degen, Albrich, Oppel, Schulz et al., 2011). During opioid withdrawal syndromes (opioid means every substance binding to opioid receptors, e.g. methadone), an activation of the HPA axis was observed (Brown et al., 2006; Kreek & Koob, 1998). Heroin-dependent patients, even after detoxification, seem to suffer from persistent hyperresponsiveness to stress factors. This heightened sensitivity of the hypothalamus and the pituitary gland to negative stimuli might contribute in part to further drug use (Kreek, LaForge, & Butelman, 2002).

1.2. Therapy of heroin dependence

The therapy of choice in heroin dependence is the maintenance treatment with methadone or buprenorphine (Soyka, Apelt, Lieb, & Wittchen, 2006). Methadone was developed in the 40s of the 20th century. Initially used as an analgesic, methadone was applied from Dole and Nyswander at the Rockefeller University in New York for treating opioid dependence twenty years later (Stoller & Bigelow, 2006). To this day, 90% of the substituted opioid-dependent patients in Switzerland have been treated with methadone (BAG, 2014). However, there are patients not responding to methadone or other treatments (Uchtenhagen, 2010). Alternative treatment strategies thus have been considered, including the prescription of diacetylmorphine (DAM, pharmaceutical heroin). In Switzerland, the heroin-assisted treatment (HAT) is available since 1994, and also in other countries HAT produces good therapy outcomes. HAT-patients showed significant improvement in their physical and mental health and psychosocial function, and the drug associated criminality declined as well (e.g. Oviedo-Joekes, Brissette, Marsh, Lauzon, Guh, Anis et al., 2009; Schmid & Müller, 2008; Uchtenhagen, 2007).

Of course, additionally to maintenance treatment, accompanying psychotherapy − particularly for heroin-dependent patients with psychiatric comorbidity − is valuable (Gerber & Walter, 2013). In order to consider the patients' self-destroying patterns and to make them acquire functional coping strategies, cognitive-behavioural interventions can be applied (Vogel, Petitjean, Borgwardt, Wiesbeck, & Walter, 2010). Further specific therapy methods as the Dialectical Behavior Therapy (DBT; Linehan, 1993) work with the patients' negative emotions (Walter, 2014; Walter, Gunderson, Zanarini, Sanislow, Grilo, McGlashan et al., 2009). Furthermore, couple and family therapy involves the patients' social environment that can support them in their everyday life (Schmidt, Gastpar, & Gaebel, 2006). Motivational Interviewing (Miller & Rollnick, 2009) and Relapse Prevention (Marlatt & Gordon, 1985) are further effective interventions for getting the patients' therapy motivation, commitment and long-term abstinence. Respect and estimation are thereby crucial elements of the therapeutic relationship.

Psychosocial support and the integration in the working environment are important units of a comprehensive treatment in individuals with substance related disorders and comorbid mental illness (Mueser et al., as cited in Stohler, 2014). The effectiveness of pharmacological therapy of comorbid psychiatric disorders is given, but possible interactions of the medicaments with opiates must thereby be considered (Stohler, 2014).

1.3.　Previous research

Previous findings have consistently shown that HPA axis function is altered in opioid dependence. First, Eisenman and colleagues observed reduced steroid levels in morphine-dependent individuals. When the drug administration was stopped, the measured parameter raised and normalized after the acute withdrawal again (Eisenman, Fraser, & Brooks, 1961; Eisenman, Fraser, & Isbell, 1958). Further examinations on stress hormones secretion in surgery patients showed the suppressing effect of opiates as well (George, Reier, Lanese, & Rower, 1974). Comparisons of ACTH and cortisol plasma levels in heroin-dependent versus healthy individuals confirmed the modified HPA axis function in opioid dependence (Ho, Wen, Fung, Ng, Au, & Ma, 1977).

A range of investigations in heroin-dependent, methadone maintained patients was realized from Kreek and colleagues at the Rockefeller University in New York. They repeatedly found a suppression of the HPA axis function in active heroin use, while an activation of the stress

hormones during withdrawal was observed. Furthermore, these neuroendocrinological anomalies normalized when middle to high methadone doses were regularly administered (Kreek, 1996 a; b).

In general, it was shown that opioids have a suppressive effect on the HPA axis function. After methadone administration, reduced cortisol concentrations and craving were observed in heroin-dependent patients (Walter et al., 2008; 2011). Opioid withdrawal, on the other hand, is associated with elevated stress hormone levels (Camí, Gilabert, San, & De La Torre, 1992). The increased stress reactivity was also observed in currently abstinent, former heroin-dependent individuals not under opioid maintenance. An appropriate long-term methadone maintenance treatment can help to modify the altered HPA axis function in heroin-dependent patients (Kreek & Koob, 1998). However, this normalization seems to be particular only. In noradrenergic stimulation, heroin-dependent, methadone maintained patients with additional cocaine use showed elevated stress hormones levels, while those without parallel cocaine consumption did not (Schluger, Borg, Ho, & Kreek, 2001). Furthermore, the comparison of heroin-dependent, methadone maintained patients with healthy controls indicated that − the clinical stabilization with methadone maintenance treatment notwithstanding − heroin-dependent individuals suffer from persistent stress hyperresponsivity (Schluger, Bart, Green, Ho, & Kreek, 2003).

Various studies showed an elevated anxiety and mood disturbance in individuals who regularly use heroin (Darke & Ross, 1997; Grenyer, Williams, Swift, & Neill, 1992). Conversely, it has been found that individuals with high anxiety tend to use drugs (Novak, Burgess, Clark, Zvolensky, & Brown, 2003; Stewart, Karp, Pihl, & Peterson, 1997). High anxiety has been shown to be associated with drug craving (Fox et al., 2005; Sinha et al., 2006). Increased aversive emotions, such as anger and sadness, and an elevated vulnerability to maladaptive emotional regulation were observed in heroin dependence (Epstein et al., 2009; Galynker, Eisenberg, Matochik, Gertmenian-King, Cohen, Kimes et al., 2007).

According to this previous research, stress and negative emotions seem to play a key role in substance use. They are closely linked to craving and withdrawal syndrome and they build the motivational core for further drug use − in order to avoid or to stop aversive feelings (Baker, Piper, McCarthy, Majeskie, & Fiore, 2004; Wang, Zhang, Wu, Liu, Hu, Chan, & Xiao, 2010).

1.4.   Current research issues

Based on the previous research findings, the association between stress, negative affect and heroin dependence can be confirmed. However, the acute effects of heroin on the HPA axis function and emotional changes have not been investigated in a randomized, controlled trial with heroin-dependent patients in stable HAT so far. In our research group, we investigated the HPA axis and emotional responses of heroin-dependent patients before and after heroin (DAM) administration in comparison with placebo (saline), as well as their responses after DAM administration or placebo compared with responses of healthy controls. Complying with ethical guidelines, we exposed the control group to the placebo condition only.

In Article 1, we hypothesized that DAM would suppress the stress hormone concentrations (ACTH and cortisol) and craving in heroin-dependent patients in contrast to elevated levels of these parameters during withdrawal (i.e. after administration of placebo). In Article 2, we expected no significant differences between ACTH and cortisol levels in heroin-dependent patients after administration of DAM compared with healthy people (i.e. we expected that the HPA axis function would normalize due to the effect of DAM). In Article 3, we hypothesized furthermore that heroin-dependent patients would show significant higher basal anxiety, depressiveness and anger compared to healthy controls. After DAM administration, we expected normalized emotional states in patients (i.e. no significant differences between measured emotions in heroin-dependent patients compared to healthy controls). After placebo, no changes in negative emotions in patients should be observed.

2.   Methods

2.1.   Study sample

Twenty-eight patients from the Division of Substance Use Disorders of the Psychiatric Hospital of the University of Basel (Switzerland) were recruited. They were aged 23−58 years (mean age = 41.3, SD = 6.6), met the DSM-IV diagnostic criteria for opioid dependence and had been in heroin-assisted treatment (standardized HAT-program in JANUS-Department of the Psychiatric Hospital of the University of Basel, Switzerland) for 6.7 years on average (SD = 4.5). Inclusion criteria were: age older than 18 years, history of intravenous heroin dependence, on current HAT for at least 6 months and unchanged dose conditions during the previous 3 months. Exclusion criteria were a positive alcohol breath test and a history of

significant medical problems or major mental disorders (other than substance use and personality disorders). Patients were asked to abstain from illicit drug (other than prescribed heroin, DAM) and alcohol use for the duration of the study.

Twenty age and gender matched healthy controls were recruited from the general population via advertisement in the same geographical area (regions Basel and Bern, Switzerland). They were screened using a semi-structured clinical interview in order to exclude possible mental or physical illness or a family history of psychiatric disorders. Criterion of exclusion were current or previous illicit drug use, a severe physical, neurological or mental illness (participants' own or in their families), and a daily alcohol consumption of more than 20 g.

All participants were native German speakers. They received written information on the examination protocol and gave their written consent. The study was approved by the local ethics committee. The socio-demographic and diagnostic characteristic of the study sample are summarized in table 1.

Table 1. Socio-demographic and diagnostic characteristics of the study sample

	Experimental group (n=28)	Control group (n=20)	p-value
Age, mean (*SD*)	41.3 (6.6)	40.3 (10.9)	0.718
Male gender, n (%)	19 (67.9)	14 (70.0)	0.875
Partnership, n (%)	9 (32.1)	15 (75.0)	0.003
Employment, n (%)	11 (39.3)	20 (100.0)	< 0.001
Disability, n (%)	9 (32.1)	0 (0.0)	0.005
Doses of DAM (mg/day)	318.6 (131.7)	-	-
Duration of heroin dependence (years)	20.8 (6.6)	-	-
Age at the first-time heroin use (years)	19.0 (3.4)	-	-
Duration of opioid maintenance (years)	6.7 (4.5)	-	-
Diagnosis of personality disorder	13 (46.4)	0 (0.0)	< 0.001
Substance use:			
- tobacco (%)	28 (100.0)	20 (100.0)	1.000
- number of cigarettes/day	21.0 (9.1)	11.5 (8.2)	< 0.001
- cocaine (%)	15 (53.6)	0 (0.0)	< 0.001
- cannabis (%)	8 (28.6)	5 (25.0)	0.53

SD = Standard Deviation.

2.2. Design and procedure

A randomized, controlled clinical trial (RCT) with a crossover design was conducted. Over two sessions, all patients were submitted to both conditions (DAM and placebo). The sequence of the injected substances was randomized. One group ($n = 14$) first received their regular dose of DAM before the beginning of the experiment, whereas the second group ($n = 14$) first received placebo (saline). Immediately after the experiment, patients received the other substance. One week later, the patients completed the second experimental condition with the opposite injections sequence. Patients were informed that they receive their regular dose of DAM either before or after the experiment. Furthermore, they knew that the second injection they obtain included an ineffective saline solution, but they were unaware of the injection sequence. Healthy controls participated in the placebo condition only. The study has been registered by the website http://clinicaltrials.gov (ID NCT01174927).

The experiment of approximately 2.5 hours per session was performed in the morning. At the beginning of the experimental session, participants' alcohol intoxication was excluded and urine samples were collected to indicate a possible drug use. After this, biochemical and psychological assessments (see below) were performed. Patients then received their first injection (DAM or placebo). Healthy controls were injected with 5 ml of saline. A presentation of stressful stimuli including decision tasks during a functional magnetic resonance imaging (fMRI) then followed. After the fMRI performance, biochemical and psychological parameters were assessed again. Patients then received the second injection (placebo or DAM, respectively) and all participants were compensated for their participation.

2.3. Materials and measurements

2.3.1. Bioanalytical and biochemical measurements

As measurements of the HPA axis response, adrenocorticotropic hormone (ACTH) in plasma and cortisol in serum and saliva were collected at baseline (at least one hour after the awakening, 7.30 am), 20 minutes and 60 minutes after the substance administration. The concentrations of heroin and its metabolites were obtained at baseline and 3, 10 and 60 minutes after the patients had received their DAM injection. The takings of blood samples and the patient-centered care were ensured by qualified specialist staff using medical materials.

The procedure of the salivary cortisol analyse is described by Walter et al. (2008). Saliva, plasma and serum samples were analysed in the medical laboratory of the University Hospital of Basel (Switzerland) using Immulite tests (Siemens, Germany). The concentrations of DAM and its metabolites (6-acetylmorphine = 6AM, morphine = M, morphine-3-β-D-glucuronide = M3G and morphine-6-β-D-glucuronide = M6G) were measured in venous ammonium-heparinized plasma obtained from 23 patients at baseline and 3, 10 and 60 minutes after the individualized heroin (DAM) injection. The analyses were performed in the Department of Clinical Research of the University of Bern (Switzerland). Sample preparation and instrumental conditions are described in detail by Bourquin, Bundeli, Lehmann and Brenneisen (1999).

2.3.2. *Psychological measurements*

Structured Clinical Interview for DSM-IV for DSM-IV Axis II Disorders (SCID-II) (First, Gibbon, Spitzer, Williams, & Benjamin, 1997) was used to assess the diagnosis of a comorbid personality disorder. The Heroin Craving Questionnaire (HCQ) was assessed to measure craving (Tiffany, Fields, Singleton, Haertzen, & Henningfield, 1993). The corresponding scale contains 9 items and measures the desire to use heroin. The State-Trait Anxiety Inventory (STAI) with two 20-item scales was administered to examine participants' anxiety (Spielberger, 1983). The state anxiety fluctuates over time and can vary in its intensity, while the trait anxiety indicates a relatively stable attribute that refers to the individual tendency to respond with anxiety to threats perceived in the environment. The 57-item State-Trait Anger Expression Inventory-2 (STAXI) was used to assess the intensity of anger as an emotional state and the degree of the disposition to experience angry feelings as a personality trait (Spielberger, 1988). The Beck Depression Inventory (BDI), in the clinical practice frequently applied self-report tool with 21 items, was used to assess the depressiveness (Beck, Erbaugh, Ward, Mock, & Mendelsohn, 1961). The 60-item Likert-scale short version of the Adjective Mood Rating Scale (AMRS, Janke & Debus, 1978) was used to assess the emotional excitation and well-being. For all applied questionnaires, good validity and reliability have consistently been demonstrated.

In order to detect possible placebo effects, 3 minutes after the substance administration the patients were asked which substance they believed they had received − DAM or placebo.

Additionally, both subjective drug effects and withdrawal symptoms were measured using a visual analogue scale (VAS) (0 = none, 10 = very strong).

2.4.   Statistical analyses

For testing the hypothesis in article 1, the following statistical methods were applied: a two-factorial repeated-measures analysis of variance (ANOVA) with two within-subject substances (DAM and placebo) and the between-subjects group membership (sequence of the administered substances) was calculated for each of the HPA axis outcome variables (plasma ACTH, serum cortisol and salivary cortisol concentrations). Cocaine use was included in the analyses as a covariate. In order to take the large range of the individual baseline hormone levels into account, ANOVAs were carried out with the differences between the baseline and post-trial measurements (i.e. before and 60 minutes after substance injection). To evaluate the stress hormone changes across the three measurement points under both conditions (baseline, 20 and 60 minutes after substance injection), pairwise contrasts of the hormone levels were calculated. Friedman's ANOVA with Wilcoxon signed-rank post hoc tests (a non-parametric analysis) was calculated for the non-normally distributed variables. To correct for the α-error accumulation, the Bonferroni correction was used. Psychometric data (HCQ scores and subjective ratings of drug effects and withdrawal symptoms) were analysed with the t-test and, where appropriate, with a non-parametric test (Wilcoxon signed-rank test) for dependent samples. The two-tailed significance level was set to $p < 0.05$.

In article 2, a repeated-measures ANOVA with two within-factors substance (DAM vs. placebo) and three time points (baseline, 20 and 60 minutes after substance injection) was calculated. The factor order of the substance was randomized between subjects. As covariates, the random order of substance administration, age, sex and personality disorder diagnosis were used. The Tukey post hoc tests were performed, when within-factors were significant. To protect against violations of sphericity, repeated-measures data were adjusted, where appropriate, for within-factor degrees of freedom using the Greenhouse-Geisser correction. The differences between patients and healthy controls were tested with t-test for the three primary endpoints (plasma ACTH, serum cortisol and salivary cortisol). Because of multiple comparisons, alpha was adjusted for 7 tests using the Bonferroni correction. As a consequence, all statistical tests were considered significant at a two-tailed level of $p < 0.0072$.

To examine the assumptions about group differences in trait variables at baseline (depression score, trait anxiety, trait anger) in article 3, a one-way analysis of variance (ANOVA) with three group levels (DAM, placebo, controls) was calculated. State variables were analyzed by repeated-measures ANOVA with two time points (at baseline and 60 minutes later), with within-subjects or group factors (DAM, placebo, controls) and a between-subjects factor. The order of the substance administration was randomized between subjects. The levels of intoxication and sedation were used as covariates. To protect against violations of sphericity, repeated-measures data were adjusted for within-factor degrees of freedom using the Huynh-Feldt corrections, where appropriate. Where the within-subject factor was significant, post-hoc planned *t*-tests comparisons were performed to identify the significant differences. All statistical tests were considered significant at a two-tailed level of $p < 0.05$.

Descriptive data were analyzed by means of unpaired *t*-tests for continuous variables and χ^2 tests for discrete variables. All analyses were computed with the statistical program SPSS for Windows (versions 17.0 and 19.0) and the graphs were created with the program SigmaPlot 11.0.

3. Results

3.1. Subjective drug effects, withdrawal symptoms and heroin craving

As expected, patients reported significantly more drug effects and fewer withdrawal symptoms after injection of DAM as after placebo ($p < 0.0001$). Only one placebo effect was observed (i.e. one patient rated saline as DAM).

As displayed in figure 1, no significant differences between HCQ scores at baseline (i.e. before any substance administration) were found ($p > 0.05$). Before and after placebo injection, HCQ scores did not differ significantly ($p > 0.05$). After DAM administration, craving dropped significantly over time ($t = 5.19$, *d.f.* $= 27$, $p < 0.0001$). Compared with placebo, significantly lower craving was reported at the end of the experimental session when patients received DAM ($t = -5.63$, *d.f.* $= 27$, $p < 0.0001$).
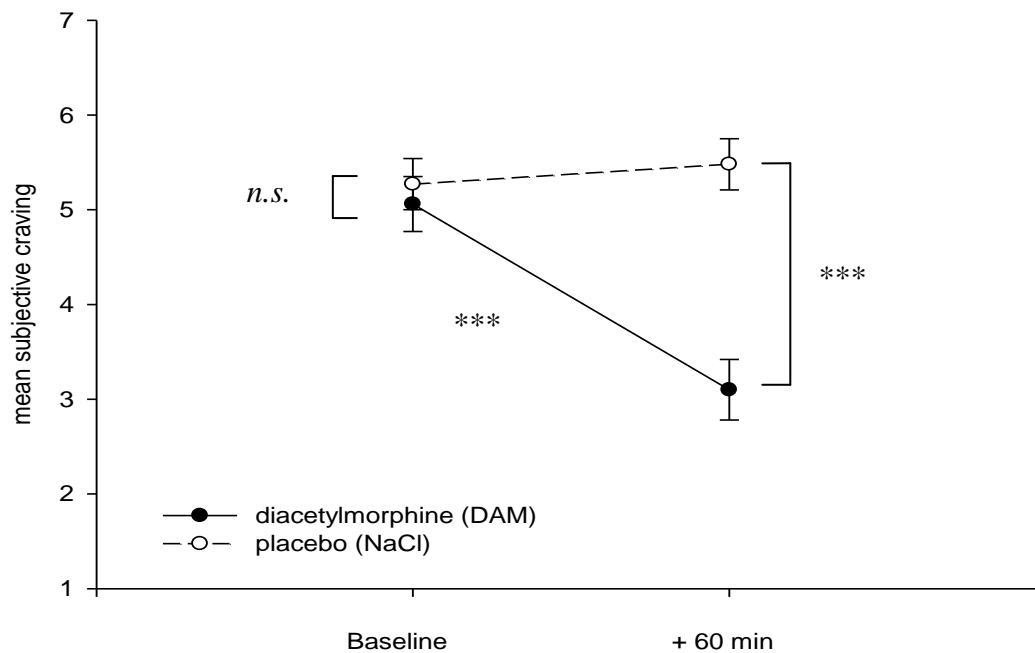
Figure 1. Patients' subjective craving (Desire to Use Heroin scale, HCQ) before and after substance administration. Means and standard errors are displayed. *** = $p < 0.0001$, *n.s.* = not significant.

At the end of the experiment (i.e. 60 minutes after substance injection), HCQ scores were significantly correlated with changes in the ACTH secretion. As expected, major heroin craving was positively related with increased ACTH concentrations when patients received placebo ($r = 0.30$, $p < 0.05$). No other significant correlation was found between the subjective craving scores and the hormonal stress response ($p > 0.05$).

3.2.   Plasma concentrations of heroin and its metabolites

Heroin (DAM) peak plasma concentrations were up to 1005 ng/ml at 3 minutes after DAM administration, due to the very short plasma elimination half-life of the substance. DAM (35−139 ng/ml) was still measurable in 3 patients at the last time point of measurement (60 minutes after injection). 6AM exhibited a concentration profile similar to DAM. M was

detectable in all patients and at all sampling time points after the administration of DAM, with a peak plasma concentration at 3 minutes (20 patients) and 10 minutes (3 patients). The decline in the plasma concentrations of M was considerably slower than the decrease observed for DAM and 6AM, which reflect the much longer elimination half-life for M compared to the acetylated compounds. At 3, 10 and 60 minutes, the concentration ranges were at 39−3885, 31−761, and 29−436 ng/ml, respectively. This indicates relatively stable plasma levels of M over a prolonged time period, with the highest inter-individual variability observed at 3 minutes. The M3G and M6G plasma concentrations steadily increased over the study period of 60 minutes and approached a plateau at the end of the experiment. Concentrations measured for M3G at the last sampling time point were between 281 and 4432 ng/ml. Considerably lower concentrations were found for M6G, ranging between of 81 and 1099 ng/ml. The plasma profiles of heroin and its metabolites are depicted in figure 2.
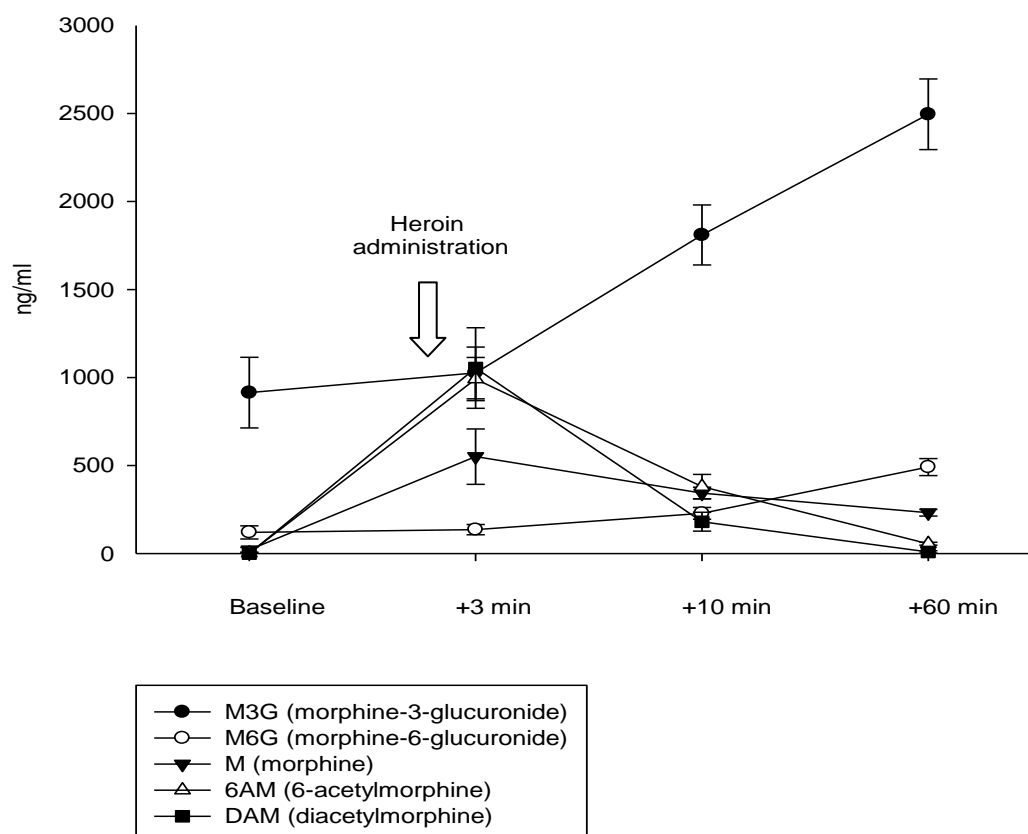
Figure 2: Plasma concentrations of heroin (diacetylmorphine, DAM) and its main metabolites in heroin-dependent patients before and after DAM injection. Means and standard errors are displayed.

3.3. Effects of heroin on HPA axis activity

3.3.1. ACTH and cortisol levels in patients

According to the analyses in article 1, DAM significantly suppressed the hormone concentrations: $F_{ACTH}(1, 25) = 8.54$, $p = 0.007$; $F_{cortisol\ serum}(1, 25) = 30.69$, $p < 0.0001$; $F_{cortisol\ saliva}(1, 25) = 11.83$, $p = 0.002$. As seen in table 2, no significant effects of cocaine use or group membership on the hormone levels were observed ($p > 0.05$).

Table 2. ANOVA for the effects of the substance (diacetylmorphine, DAM) on stress hormone levels and the interactions between substance and cocaine abuse and between substance and group membership

Source	SS	df	MS	F	p-value
ACTH					
Substance	12696.98	1	12696.98	8.54	0.007
Substance x cocaine-abuse	681.45	1	681.45	0.46	0.505
Substance x group	960.19	1	960.19	0.65	0.429
Error (Substance)	37151.20	25	1486.05		
Cortisol serum					
Substance	515684.12	1	515684.12	30.69	0.000
Substance x cocaine-abuse	7042.94	1	7042.94	0.42	0.523
Substance x group	2352.60	1	2352.60	0.14	0.711
Error (Substance)	420064.11	25	16802.56		
Cortisol saliva					
Substance	7131.07	1	7131.07	11.83	0.002
Substance x cocaine-abuse	3.76	1	3.76	0.01	0.938
Substance x group	1916.02	1	1916.02	3.18	0.087
Error (Substance)	15070.16	25	602.81		

SS = Sum of Squares; *df* = degrees of freedom; *MS* = Mean Square, x = Interaction.

The pairwise comparisons of the hormone levels showed significant reductions in plasma ACTH, serum cortisol and salivary cortisol concentrations over time after the DAM administration ($p < 0.0001$). In the placebo-condition, only plasma ACTH increased

significantly, namely between 20 and 60 minutes after the injection ($p < 0.01$). Cortisol levels did not increase significantly after placebo injection ($p > 0.05$). No significant differences between the baseline hormone levels were found ($p > 0.05$). Figures displaying the results can be seen in article 1 in the appendix.

The repeated measures ANOVA calculated in article 2 showed significant substance (DAM vs. saline) and time interactions for ACTH ($F = 11.21$, $p = 0.001$), serum cortisol ($F = 45.59$, $p < 0.001$) and salivary cortisol ($F = 20.16$, $p < 0.001$) concentrations in heroin-dependent patients. There were significant time effects for ACTH ($F = 6.06$, $p = 0.014$) and serum cortisol ($F = 16.46$, $p = 0.001$) levels. According to the post-hoc tests, ACTH decreased significantly from baseline to 20 minutes ($F = 5.54$, $p < 0.05$) and from 20 to 60 minutes after administration of DAM ($F = 40.65$, $p < 0.0001$). Serum cortisol ($F = 51.50$, $p < 0.0001$) and salivary cortisol ($F = 12.99$, $p = 0.001$) decreased from baseline to 20 minutes after DAM administration, and serum cortisol ($F = 42.50$, $p < 0.0001$) and salivary cortisol ($F = 26.70$, $p < 0.0001$) decreased again from 20 to 60 minutes after DAM administration. There was no significant influence of covarites (random order of substance administration, age, sex, diagnosis of personality disorder) on stress hormone levels.

3.3.2. ACTH and cortisol levels in patients compared with healthy controls

At baseline, ACTH concentrations were significantly higher in patients than in healthy controls ($t = 2.96$, $df = 37.52$, $p = 0.005$). 60 minutes after the substance administration, serum cortisol and salivary cortisol did not differ between heroin-dependent patients and healthy controls when patients received DAM. ACTH concentrations were significantly lower 60 minutes after DAM administration in patients than in healthy controls ($t = -3.55$, $df = 46$, $p = 0.001$). When patients received placebo, their ACTH ($t = 4.98$, $df = 29.97$, $p < 0.0001$), serum cortisol ($t = 3.87$, $df = 46$, $p < 0.0001$) and salivary cortisol ($t = 4.01$, $df = 43.17$, $p < 0.0001$) concentrations were significantly higher than in healthy controls at the end of the experiment.

As illustration, figure 3 depicts the concentrations of salivary cortisol. Figures showing the differences in all measured stress hormone levels between heroin-dependent patients and healthy controls are shown in article 2 in the appendix.
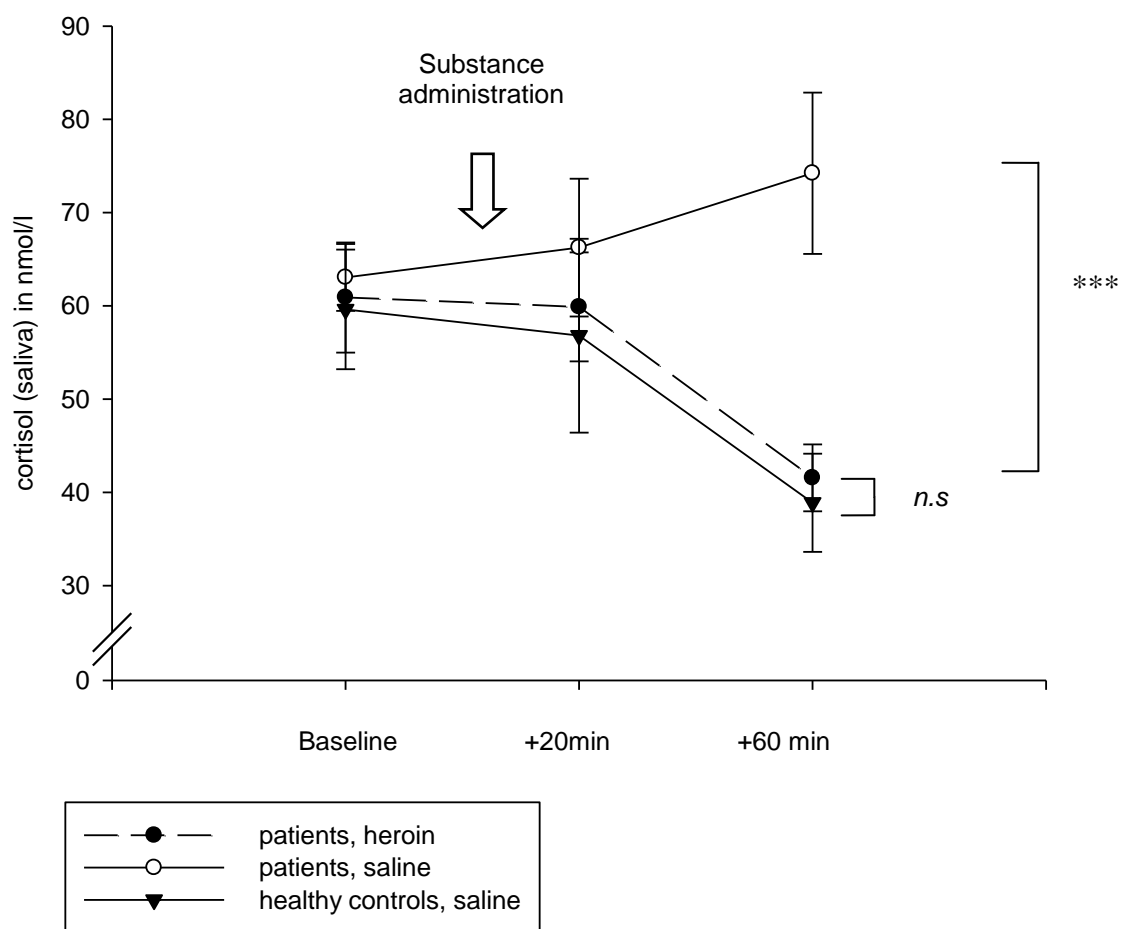
Figure 3: Salivary cortisol concentrations in heroin-dependent patients before and after heroin (diacetylmorphine, DAM) or placebo (saline) injection and in healthy controls after saline injection. Means and standard errors are displayed. *** = $p < 0.001$, *n.s.* = not significant.

3.4. Effects of heroin on emotions

3.4.1 *Depressiveness, trait anxiety and trait anger at baseline*

Before substance administration, heroin-dependent patients exhibited significantly higher depression scores than healthy controls ($t = -7.10$, $df = 46$, $p < 0.0001$), with an average score of 14 (according to BDI, the cut off score for mild depression), and a higher trait anxiety ($t = -5.75$, $df = 46$, $p < 0.0001$). The trait anger score did not differ significantly between the groups.

3.4.2. Effects of heroin on state anxiety and state anger

Repeated-measures ANOVA carried out in article 3 showed a significant time effect ($F = 13.06$, $p = 0.001$), a significant group effect ($F = 14.71$, $p = < 0.0001$) and a significant interaction effect ($F = 5.18$, $p = 0.008$) for state anxiety. There were no significant effects of subjective intoxication or sedation. State anxiety decreased in patients after DAM administration ($t = 6.16$, $df = 27$, $p < 0.0001$), but not after placebo. After DAM, patients did not differ in their state anxiety from healthy controls at the end of the experiment. After placebo, patients showed higher state anxiety than healthy controls ($t = 5.06$, $df = 45$, $p < 0.0001$).

State anger showed a significant group effect ($F = 14.71$, $p = < 0.0001$) and a significant interaction effect ($F = 5.18$, $p = 0.008$). The subjective intoxication and sedation had no significant influence. After the administration of DAM, state anger decreased significantly in patients ($t = 6.16$, $df = 27$, $p < 0.0001$), whereas it increased after placebo ($t = -2.11$, $df = 27$, $p = 0.044$). After the placebo administration, patients showed significantly higher state anger than healthy controls ($t = 2.83$, $df = 46$, $p = 0.007$).

3.4.3. Effects of heroin on mood

A significant group effect ($F = 11.70$, $p = < 0.0001$) and a significant interaction effect ($F = 21.98$, $p < 0.0001$) were observed for emotional excitation. The covariates intoxication and sedation had no significant influence. After DAM, but not after placebo, the emotional excitation levels in patients decreased significantly ($t = 4.62$, $df = 27$, $p < 0.0001$) and they differed no longer significantly from healthy controls ($p > 0.05$). Furthermore, ANOVA showed a significant group effect ($F = 13.03$, $p = < 0.0001$) and a significant interaction effect ($F = 4.20$, $p = 0.019$) for well-being as well. Also in this case, no significant influence of the covariates intoxication and sedation was detected. The well-being scores in patients increased significantly after DAM administration ($t = -3.58$, $df = 27$, $p = 0.001$) and patients rated their well-being higher after DAM than after placebo administration ($t = 3.31$, $df = 27$, $p = 0.002$). After DAM, patients' well-being reached the level of healthy controls ($p > 0.05$).

The described results of the effect of heroin on emotions are displayed in table 2 in article 3 in the appendix.

4. Discussion

4.1. Strengths and limitations

The issue of the present study was to examine the acute effects of diacetylmorphine (pharmaceutical heroin, DAM) on the HPA axis function and emotional state in heroin-dependent patients. Presumably, this is the first study on effects of DAM administration on the HPA axis and emotional response in heroin-dependent patients compared to placebo and to healthy controls in a controlled experimental setting.

The analyses showed significant decreases in ACTH and cortisol concentrations and in the HCQ (heroin craving) scores in heroin-dependent patients after heroin (DAM) administration in comparison to placebo. There was no significant interaction between the injected substance and additional cocaine use or between the substance and the sequence of substance administration, indicating that the damping of the HPA axis is due to DAM. Moreover, patients' stress hormone levels after DAM administration did not differ (cortisol) or were even lower (ACTH) than those from healthy controls. In the placebo condition, however, the stress hormone levels were higher in patients than in healthy controls. Furthermore, irrespective of the perceived intoxication and sedation levels, negative emotions decreased, whereas well-being increased in heroin-dependent patients after DAM administration. When patients received DAM, their emotional experience did not differ from those of healthy controls. After placebo, levels of patients' negative emotions were higher in comparison with healthy controls. These findings demonstrate the acute suppressive effect of heroin (DAM) on the HPA axis activity and its alleviating influence on negative emotions and heroin craving in chronic heroin-dependent, DAM-maintained patients. Also on stable opioid maintenance treatment (HAT), heroin-dependent patients seem to show a different stress responses than healthy people when they do not receive their regular opioid (DAM) dose.

The observed plasma concentrations of heroin and its metabolites revealed the short half-life of heroin (DAM) with a plateau phase, explaining the immediate blunting effect of DAM on the stress hormones secretion and negative emotions. The relatively stable plasma level over a prolonged time period of the active metabolite morphine, however, underscores the suppressive effect of DAM even one hour after administration (Kosel, Noss, Hämmig, Wielepp, Bundeli, Heidbreder et al., 2008).

The elevated HPA axis response observed in heroin-dependent patients after placebo supports previous results showing that HPA axis activity merely partial normalized in methadone-maintained, heroin-dependent patients compared to active and to former heroin users (Kreek et al., 2002). According to findings in the present study, heroin-dependent patients in HAT seem to need their regular DAM doses to suppress the hyperresponsiveness of the HPA axis sustainably. Furthermore, the elevated hormone levels (ACTH) before substance administration in patients compared to healthy controls probably reflects the beginnings of withdrawal symptoms, given that patients had not received their dose of DAM at that point of time. As expected, patients' withdrawal levels decreased after DAM administration, but not after placebo.

In previous studies, opioid withdrawal was associated with an elevated stress hormone secretion (Camí et al., 1992; Volavka, Cho, Mallya, & Baumann, 1979). In the present study, however, the increase in the hormone levels after placebo was only by trend. Solely ACTH levels increased significantly between 20 and 60 minutes after placebo injection, but the main time effect was non-significant as well. Hence, this finding does not support the idea that opioid withdrawal is associated with an activation of the HPA axis. This can possibly be explained by the patients' long-standing maintenance treatment (HAT) as well as their knowledge that they would receive their regular DAM dose not later than at the end of the experiment. Although they reported withdrawal symptoms, patients may not have experienced intense somatic withdrawal in fact. The significant correlation between the craving scores and the changes in ACTH levels at the end of the experiment showed the relationship between patients' subjective feeling and their endocrine response, suggesting that the greater the subjective withdrawal, the higher the stress hormone concentrations and vice versa. Of course, this relationship does not allow the conclusion, that changes in the HPA response have a significant impact on the subjective experience of craving. The elevated ACTH levels might nevertheless be a possible explanation for the higher subjective craving scores.

In contrast to the results of the present study, Wisniewski, Brown, John, Cofranceso, Golub, Ricketts et al. (2006) found elevated basal cortisol levels in active drug users. According to the authors, these findings might reflect withdrawal symptoms during the study as well as the combination of heroin and cocaine commonly used by illicit drug users. Therefore, the regularity and availability of DAM as well as other psychological and supporting elements of the HAT may have been relevant factors influencing patients' stress response, resulting in a relative stability of the stress hormones secretion during the experiment, even in the placebo

condition. Furthermore, in the present study, cocaine-dependent patients were not included in the recruitment and all patients who participated denied cocaine use during the last day before the experiment. Hence, the expected counteracting effects of cocaine – an increased activation of the HPA axis − (Sinha et al., 2006), were not observed here. For more clarity, the association between opioid withdrawal, heroin craving and HPA axis activity should next be examined by including heroin-dependent individuals not in stable opioid maintenance treatment and without concurrent cocaine use. However, the recruitment of such a sample and the study realization could prove difficult, due to the common polysubstance use observed by the majority of heroin-dependent individuals (Wisniewski et al., 2006).

Consistent with previous findings (Wang et al., 2010), the observed higher basal levels of anxiety and depressiveness in heroin-dependent patients compared to healthy controls indicate a possible affective vulnerability with a reduced stress tolerance and a restricted ability to cope with emotional stress. After DAM administration, negative emotions (anxiety and anger) decreased significantly in heroin-dependent patients. This dampening effect on the emotional feeling supports the acute emotional regulation character of DAM and may therefore be a relevant maintaining factor in further drug use. In accordance with these results, functional imaging studies provided evidence for an altered processing of emotional stimuli in opioid users (Aguilar de Arcos, Verdejo-Garcia, Ceverino, Montanez-Pareja, Lopez-Juarez, Sanchez-Barrera et al., 2008) and for neural alterations in their brain function and structure (Volkow, Fowler, & Wang, 2003; Wrege & Borgwardt, 2014). Heroin (DAM) could therefore be an effective instrument in correcting this maladaptive emotion regulation in heroin-dependent patients. Moreover, due to the observed increase in the well-being ratings after DAM administration, but not after placebo, heroin consumption could be considered as a kind of self-medication (Khantzian, 1997), as patients may use heroin in order to handle their emotional imbalance and stress vulnerability based on the pathological brain changes (Kalivas & Volkow, 2005; Volkow et. al, 2003).

The main strength of the present study is the randomized, controlled cross-over design and the adequate sample size allowing the control of confounding variables and sequence effects. Such study design can only be realized in countries with heroin-assisted treatment (HAT) programs, including Switzerland. On the other hand, the stressful stimuli presented in the fMRI-session were not a valid stress test, as is for example the Trier Social Stress Test (Kirschbaum, Pierke, & Hellhammer, 1993). So far there is no standardized picture set regarding drugs that would be used to examine stress reactions in substance users. This

limitation could be mitigated by the fact that fMRI-scanning has been demonstrated to be a stressful experience associated with elevated cortisol concentrations in healthy people and depressive patients (Muehlhan, Lueken, Wittchen, & Kirschbaum, 2011; Peters, Cleare, Papadopoulos, & Fu, 2011). In substance use disorders, psychosocial stress is generally considered to be a predictive factor for relapse (Walter, Gerhard, Duersteler-MacFarland, Weijers, Boening, & Wiesbeck, 2006).

4.2. Clinical implications

As the present study showed, short-acting opioids such as heroin (DAM, respectively) seem to reduce the patients' heightened stress responsivity, their heroin craving and aversive emotions. The above mentioned limitations notwithstanding, the results hence support the efficacy of heroin-assisted treatment (HAT) by suggesting that heroin (DAM) may contribute to a normalization of the hyperreactivity to stress factors and to the maladaptive emotional processing in heroin-dependent patients.

Several previous studies have already provided evidence of the positive effects of DAM maintenance in those heroin-dependent patients, for whom methadone maintenance treatment (MMT) or abstinence-orientated (drug free) therapy had been unsuccessful (i.e. Rehm, Gschwend, Steffen, Gutzwiller, Dobler-Mikola, & Uchtenhagen, 2001; van den Brink, Hendricks, Blanken, Koeter, van Zwieten, & van Ree, 2003). Heroin-assisted treatment (HAT) is now regarded as an established treatment for severe opioid dependence in Switzerland and the Netherlands (Uchtenhagen, 2010). Moreover, recent research has indicated the efficacy of HAT even in heroin-dependent patients with no previous maintenance experience (Haasen, Verthein, Eiroa-Orosa, Schäfer, & Reimer, 2010). However, there is also a risk of negative side effects in HAT. Based on the intravenous administration of DAM, respiratory depression or epileptic seizure can occur (Stohler, Dürsteler, Störmer, Seifritz, Hug, Sattler-Mayr et al., 1999). Under medical supervision and professional practice of HAT, however, such incidents can be avoided. In addition to the injectable form, oral administration of DAM is also possible (Frick, Rehm, Zullino, Fernando, Wiesbeck, Amman et al., 2010).

Apart from the direct effects of DAM, HAT may offer further stress reducing factors. The psychosocial support and medical care, the guaranty of the daily opioid dosis and therefore the reduction of drug related criminality and infectious diseases as well as the daily rhythm

and the room for social interchange could make an essential contribution to patients' compliance and positive therapy outcome. DAM may therefore be understood as a protective factor helping heroin-dependent patients to counteract with their heightened stress sensitivity. It can furthermore be considered as a precondition for an extensive psychosocial treatment program, such as HAT, that supports chronic heroin-dependent patients to improve their general state of health and their psychosocial situation (Gerber, Borgwardt, Gerhard, Riecher-Rössler, Wiesbeck, & Walter, 2011).

4.3.   Conclusion and further research

The present study indicates that heroin (DAM) suppresses significantly the HPA axis activity and alleviates the negative emotions including heroin craving and withdrawal syndrome in chronic heroin-dependent patients in a stable opioid maintenance treatment (HAT). A regular DAM administration may therefore protect heroin-dependent patients against their heightened stress responsivity and their vulnerability to negative emotional experiences. For those chronic heroin-dependent patients who initially do not profit from other therapies, HAT is an effective treatment which complements the therapeutic options for opioid dependence, to date only in a few countries. Further research on the heroin (DAM) effect on the physical and emotional stress response in chronic heroin-dependent patients could contribute to the optimization of HAT and would still underscore its benefits.

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Appendix

Author´s contribution

In the present study (SNSF, 32003B-127544), I was responsible for the following tasks and areas of research:

Assistance in planning and carrying out the study realization by preparing the study material (questionnaires, medical and other equipment), collecting, entering and analysing the data, coordinating the study process and carrying out different administrative and organizational tasks. In collaboration with other co-authors, I wrote publications and created further research contributions (poster, oral presentations). Within the framework of the study, I also participated in scientific events at a domestic and international level.

Original articles

The Impact of Diacetylmorphine on Hypothalamic-Pituitary-Adrenal Axis Activity and Heroin Craving in Heroin Dependence

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Abstract

Background/Aim: Heroin dependence is a chronic relapsing disorder characterized by the compulsion to seek and use heroin. Stress and craving are seen as key factors for heroin use. Moreover, altered hypothalamic-pituitary-adrenal (HPA) axis function has been frequently reported. However, the acute effects of diacetylmorphine (DAM) on HPA axis activity and craving have not been investigated in a controlled study. The present randomized controlled study examined whether DAM administration differs from placebo (saline) administration with regard to HPA axis response and heroin craving. *Methods:* In a crossover experiment, 28 DAM-maintained heroin-dependent patients were first injected with DAM and then saline, or the converse. Plasma adrenocorticotropic hormone (ACTH) and cortisol in saliva and serum were measured at baseline and 20 and 60 min after both injections. Heroin craving was measured at baseline and 60 min after both injections, by means of the Heroin Craving Questionnaire. *Results:* Compared to saline, DAM administration induced a significant decrease in plasma ACTH (p < 0.01), serum cortisol (p < 0.0001) and saliva cortisol (p < 0.01), as well as in craving (p < 0.0001), over time. *Conclusion:* Since acute DAM administration suppresses the stress response, DAM-assisted treatment may be an effective alternative to methadone maintenance in stress-sensitive heroin-dependent patients.

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Introduction

Opioid dependence is a chronic relapsing brain disorder characterized by compulsive seeking and use of opioids despite the negative consequences [1]. Drug-related cues, stress or negative mood are associated with craving [2–5]. Several previous studies have shown the relevance of stress and hypothalamic-pituitary-adrenal (HPA) axis dysfunction in substance use disorders [6–11].

The first findings on the suppression of adrenocortical functions in opiate dependence were reported by Eisenman et al. [12, 13] in the 1950s and 1960s in Lexington,

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Ky., USA. They found reduced urinary levels of 17-ketosteroids [12] and reduced plasma levels of 17-hydroxycorticosteroids [13] during a period of addiction in men, in comparison to a phase of nonaddiction. Moreover, these levels increased upon discontinuation of morphine. After detoxification, these levels returned to the preaddiction range [12, 13], indicating that stress hormone secretion was depressed during opioid addiction and elevated during withdrawal. Further research has shown that opioids administered during surgery suppress HPA axis activity [14, 15]. Furthermore, heroin-dependent subjects exhibited lower plasma levels of adrenocorticotropic hormone (ACTH) and cortisol when compared with healthy individuals [14, 16], thus providing further evidence that HPA axis activity is suppressed during active opioid dependence. On the other hand, recent studies suggest that substance use disorders are associated with elevated cortisol levels and depressive symptoms [17]. The increased HPA axis activity might constitute a vulnerability to the development of substance use disorders and relapse, and this relationship seems to be influenced by stressful life experiences [18, 19].

The altered HPA axis function in substance use disorders is related to early life stress [20, 21]. Patients reporting childhood trauma showed increased cortisol and decreased ACTH concentrations during withdrawal, which possibly reflect a persistent blunting of the HPA axis function as well as its hypersensitive reaction to acute stress in traumatized, alcohol-dependent patients [20]. Moreover, higher cortisol and ACTH plasma levels were found in abstinent heroin- and cocaine-dependent patients in comparison to healthy control subjects without a history of illicit drug use and childhood trauma [21].

Opioid withdrawal is associated with increased stress hormone levels [22]. Research on opioid antagonists (e.g. naloxone) further supports this finding [23, 24]. However, elevated stress reactivity was also found in currently abstinent, formerly heroin-dependent individuals not under opioid maintenance, which could be related to heightened craving and relapse [25–27]. Opioid agonists, on the other hand, are associated with a reduction in stress hormone secretion [28, 29]. In preliminary studies, our group also found that opioids suppress cortisol concentrations in heroin-dependent patients and reduce craving after methadone administration [30, 31].

Although previous findings have consistently shown that HPA axis function is modified in heroin dependence and that opioids suppress stress hormone release, there have been few experimental studies and these have generally focused on the effects of methadone [28, 29]. However, methadone maintenance treatment (MMT) is not the only treatment for severe heroin dependence, as heroin-assisted treatment (HAT), involving the prescription of pharmaceutical heroin (diacetylmorphine, DAM), medical attendance and psychosocial support, is also effective [32]. Chronic heroin-dependent patients who initially do not benefit sufficiently from MMT and abstinence-oriented (drug-free) treatments respond well to treatment with DAM and improve significantly in terms of mental and physical health and psychosocial functioning, mainly assessed as reduction in crime and concurrent use of illegal substances [33–39].

The present randomized controlled trial examined HPA axis function in opioid dependence after DAM administration. Our aim was to investigate the acute effects of DAM on HPA axis activity, subjective craving and withdrawal symptoms in chronic heroin-dependent patients. We hypothesized that DAM would suppress ACTH and cortisol concentrations and heroin craving, in contrast to the increases in these parameters observed during withdrawal.

Materials and Methods

Study Sample

Twenty-eight patients (67.9% men, n = 19) were recruited from patients at the Division of Substance Use Disorders of the Psychiatric Hospital of the University of Basel. They were aged 23–58 years (mean age 41.3 years, SD 6.6), met the DSM-IV diagnostic criteria for opioid dependence and had been in HAT for a mean period of 6.7 years (SD 4.5). Exclusion criteria included a positive breath alcohol test and a history of significant medical problems or major mental disorders (other than substance use and personality disorders). All patients received written information on the examination protocol and gave their written consent. The study was approved by the local ethics committee.

Procedure

The present study is a part of a randomized controlled clinical trial. It has been registered on the website http://clinicaltrials.gov (ID NCT01174927). All patients were submitted to both conditions in a crossover design. The sequence of the injected substances [DAM and saline (NaCl) as placebo] was randomized. One group (n = 14) first received their daily dose of DAM before the beginning of the experiment, whereas the second group (n = 14) first received placebo (NaCl). The patients were blinded to the substance. DAM was provided by the Swiss Federal Office of Public Health in the form of the hydrochloride salt. This was dissolved in water (1:9) on site and aspirated into a syringe, which was adapted to the evacuated infusion system. Patients of the second group were given their daily dose of DAM immediately after the experiment. The test period lasted approximately 2.5 h, including stressful stimuli during a functional magnetic resonance imaging

Table 1. Sociodemographic and diagnostic characteristics of the study sample (n = 28)

Characteristic	Mean	SD
Age, years	41.3	6.6
Male gender	19 (67.9)	
Education, years	10.4	2.5
In relationship	9 (32.1)	
Employed	11 (39.3)	
Disability	9 (32.1)	
Doses of DAM, mg/day	318.6	131.7
Methadone maintenance	13 (46.4)	
Doses of methadone, mg/day	13.4	17.4
Duration of dependence, years	20.8	6.6
Age at first-time heroin use, years	19.0	3.4
Duration of opioid maintenance, years	6.7	4.5
Substance abuse		
Tobacco	28 (100.0)	
Number of cigarettes/day	21.0	9.1
Cocaine	15 (53.6)	
Cannabis	8 (28.6)	

Values in parentheses represent percentages.

(fMRI) examination. One week later, the patients completed the alternative treatment, with the opposite sequence of substance injections. Both sessions were performed in the morning.

Biochemical Measurements
ACTH and cortisol were taken as measures of the stress response. Samples were collected at baseline (at least 1 h after awakening, 7.30 a.m.) and 20 min (9.00 a.m.) and 60 min after substance administration (10.30 a.m.). Salivary cortisol was analyzed with a time-resolved immunoassay with fluorescence detection, as described elsewhere [30]. Total cortisol concentrations were measured in serum with the Immulite 2000 cortisol test (Siemens, Germany). ACTH was measured in EDTA plasma with the ACTH Immulite test (Siemens). Interassay and intra-assay coefficients of variance were below 10% for all analyses.

Psychological Measurements
Psychological data were collected at the beginning and the end of the experiment. The Heroin Craving Questionnaire (HCQ) [40] was used to measure heroin craving. A reliability of α = 0.94 was calculated. The corresponding scale contains 9 items and measures the desire to use heroin.

In order to detect possible placebo effects, 3 min after the substance administration the patients were asked which substance they believed they had received, i.e. DAM or placebo. Additionally, both subjective drug effects and withdrawal symptoms were measured using a visual analogue scale (0 = none, 10 = very strong).

Statistical Analyses
For each of the outcome variables (plasma ACTH, serum cortisol, salivary cortisol concentrations), a two-factorial repeated-measures analysis of variance (ANOVA) was calculated, with two within-subject substances (DAM/placebo) and the between-subjects group membership (sequence of the administered substances). Cocaine use was included in the analyses as a covariate. In order to take the large range of individual baseline hormone levels into account, ANOVAs were carried out with the differences between the baseline and post-trial measurements (i.e. before and 60 min after substance injection). To evaluate the stress hormone changes across the 3 measurement points under both conditions (baseline and 20 and 60 min after substance injection), pairwise contrasts of the hormone levels were calculated. For the non-normally distributed variables, a nonparametric analysis (Friedman's ANOVA with Wilcoxon signed-rank post hoc tests) was calculated. The Bonferroni correction was used to correct for the α-error accumulation.

Psychometric data (HCQ scores and subjective rating of drug effects and withdrawal symptoms) were analyzed with the t test and, where appropriate, with a nonparametric test (Wilcoxon signed-rank test) for dependent samples.

All analyses were computed with the statistical program SPSS 19.0. Graphs were created with SigmaPlot 11.0. The two-tailed significance level was set to $p < 0.05$.

Results

Demographic and Clinical Variables
As shown in table 1, 8 patients (28.6%) tested positive for cannabis and 15 patients (53.6%) for cocaine at one or both measurements. No significant differences were observed between the two groups in terms of diagnostic and sociodemographic variables ($p > 0.05$). Table 1 gives an overview of the characteristics of our patient sample.

Drug Effects, Withdrawal Symptoms and Heroin Craving
As expected, significantly more drug effects and fewer withdrawal symptoms were reported after injection of DAM than with placebo ($p < 0.0001$). Only one placebo effect was observed, as one patient rated NaCl as DAM.

No significant differences between HCQ scores at baseline (i.e. before any substance administration) were found ($p > 0.05$). Before and after placebo injection, HCQ scores did not differ significantly either ($p > 0.05$). However, after DAM administration, craving dropped significantly over time (t = 5.19, degrees of freedom = 27; $p < 0.0001$). Compared with placebo, significantly lower craving was reported at the end of the sequence when patients received DAM (t = –5.63, degrees of freedom = 27; $p < 0.0001$) (fig. 1).

At the end of the experiment (i.e. 60 min after substance injection), HCQ scores were significantly associated with changes in ACTH secretion. As expected, major heroin craving was positively related with increased
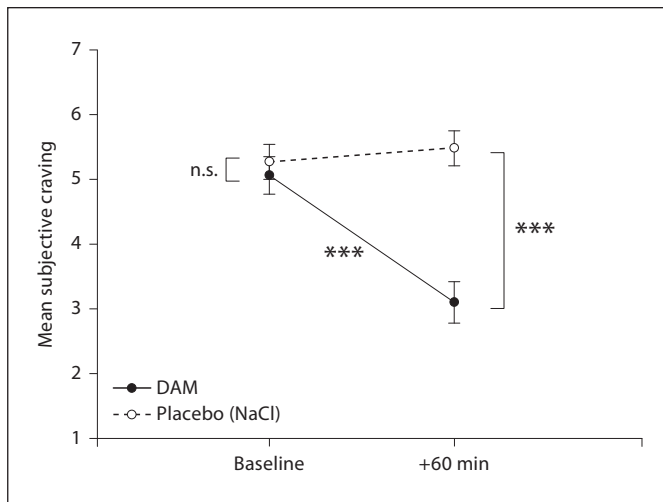
Fig. 1. Patients' subjective craving (Desire to Use Heroin scale, HCQ) before and after substance administration. Means and standard errors are displayed. *** p < 0.0001, n.s. = not significant.
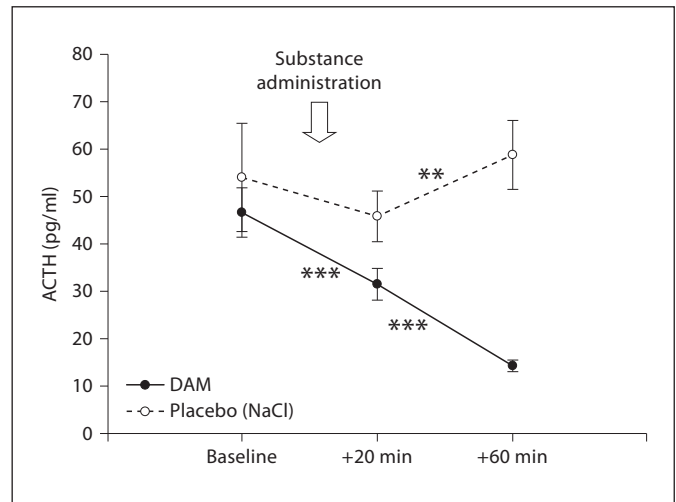
Fig. 2. ACTH concentration in DAM (heroin)-maintained patients after DAM (heroin) or placebo (saline) injection. Means and standard errors are displayed. ** p < 0.01, *** p < 0.0001.

ACTH concentrations when patients received placebo (r = 0.30; p < 0.05). No other significant correlation was found between the subjective craving scores and the hormonal stress response (p > 0.05).

HPA Axis Activity

DAM significantly suppressed hormone concentrations, as follows: ACTH, F(1, 25) = 8.54, p = 0.007; cortisol serum, F(1, 25) = 30.69, p < 0.0001, and cortisol saliva, F (1, 25) = 11.83, p = 0.002. No significant effects on the hormone levels of cocaine use or group membership were observed (p > 0.05) (table 2).

The pairwise comparisons of the hormone levels showed significant reductions in plasma ACTH, serum cortisol and saliva cortisol concentrations over time after DAM administration (p < 0.0001). After placebo administration, only plasma ACTH increased significantly, between 20 and 60 min after the injection (p < 0.01). Cortisol levels did not increase significantly after placebo injection (p > 0.05). No significant differences between the baseline hormone levels were found (p > 0.05) (fig. 2–4).

Discussion

The present study examined the acute effects of DAM (pharmaceutical heroin) on HPA axis function and heroin craving in a controlled experimental setting. There

were significant decreases in ACTH and cortisol concentrations and in HCQ scores with DAM in comparison to placebo, demonstrating that DAM suppressed HPA axis activity and reduced heroin craving in chronic heroin-dependent, DAM-maintained patients.

The suppressive effect of opioids in general [12–16] and of methadone in particular [25, 30] on stress hormone secretion and subjective craving has already been shown. Our recent uncontrolled study also found reduced cortisol concentrations in heroin-dependent patients after they had received DAM [31]. This has now been confirmed for the first time in a randomized, controlled, crossover study. There was no significant interaction between the injected substance and concurrent cocaine use or the sequence of administration, indicating that the suppression of the HPA axis is solely due to DAM administration, there is no significant carryover effect and cocaine abuse is irrelevant [41]. Our results thus confirm the attenuating effect of acute opioid administration on the HPA axis response. Further studies should investigate whether maintenance treatment with DAM also normalizes diurnal stress hormone secretion in opioid-dependent patients.

In previous studies, opioid withdrawal was associated with increased stress hormone secretion [22–24]. However, in contrast to the highly significant continuous decline in the hormone concentrations after DAM administration, the increase in the hormone levels after placebo
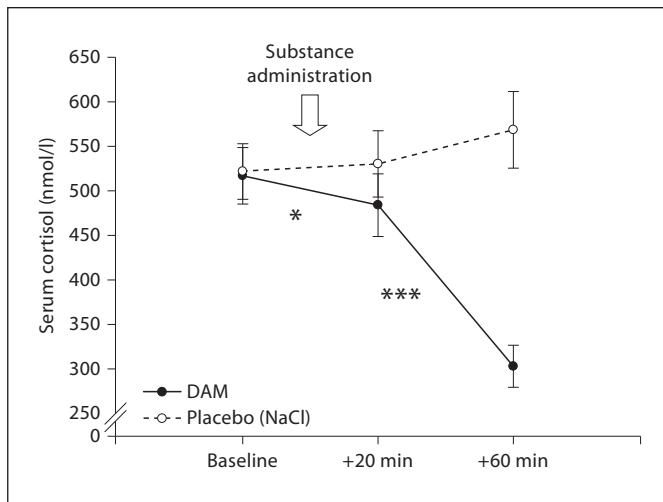
Fig. 3. Serum cortisol concentration in DAM (heroin)-maintained patients after DAM (heroin) or placebo (saline) injection. Means and standard errors are displayed. * p < 0.05, *** p < 0.0001.
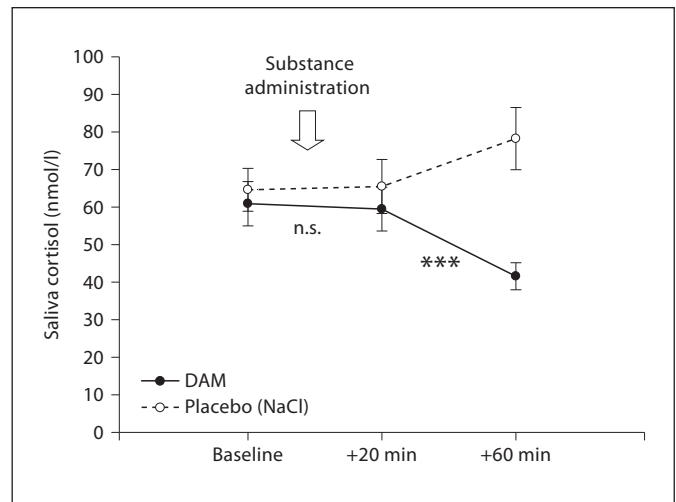
Fig. 4. Saliva cortisol concentration in DAM (heroin)-maintained patients after DAM (heroin) or placebo (saline) injection. Means and standard errors are displayed. *** p < 0.0001, n.s. = not significant.

Table 2. ANOVA for the effects of the substance (DAM) on stress hormone levels and the interactions between substance and cocaine abuse and between substance and group membership

	SS	d.f.	MS	F	p value
ACTH					
Substance	12,696.98	1	12,696.98	8.54	0.007
Substance × cocaine abuse	681.45	1	681.45	0.46	0.505
Substance × group	960.19	1	960.19	0.65	0.429
Error (substance)	37,151.20	25	1,486.05		
Cortisol serum					
Substance	515,684.12	1	515,684.12	30.69	0.000
Substance × cocaine abuse	7,042.94	1	7,042.94	0.42	0.523
Substance × group	2,352.60	1	2,352.60	0.14	0.711
Error (substance)	420,064.11	25	16,802.56		
Cortisol saliva					
Substance	7,131.07	1	7,131.07	11.83	0.002
Substance × cocaine abuse	3.76	1	3.76	0.01	0.938
Substance × group	1,916.02	1	1,916.02	3.18	0.087
Error (substance)	15,070.16	25	602.81		

SS = Sum of squares; d.f. = degrees of freedom; MS = mean square; × = interaction.

in our study was slight or nonsignificant. Only ACTH levels increased significantly between 20 and 60 min after placebo injection, but the main time effect was nonsignificant as well. Hence, our findings do not support the idea that opioid withdrawal is associated with activation of the HPA axis. These results can possibly be explained

by the patients' long-standing heroin-assisted treatment (HAT). Moreover, patients in both groups knew that they would receive their daily DAM dose at the end of the experiment at the latest. Although they reported withdrawal symptoms, they may not have experienced intense somatic withdrawal. Wisniewski et al. [17] found elevated

basal cortisol levels in active drug users, which might reflect withdrawal symptoms during the study as well as the combination of heroin and cocaine commonly used by illicit drug users. Therefore, in our study the regularity of DAM administration and its availability, as well as other psychological factors associated with the HAT, including psychosocial support, may have been relevant factors influencing the patients' stress response, resulting in relative stability of stress hormone secretion during the experiment, even in the placebo condition. The association between opioid withdrawal and HPA axis activity in heroin-dependent patients should next be examined by including heroin-dependent individuals without opioid maintenance treatment.

The significant correlation between the craving scores and the changes in ACTH levels at the end of the experiment showed the relationship between the patients' subjective feeling and their endocrine response, suggesting that the greater the subjective withdrawal, the higher the stress hormone concentrations and vice versa. However, this relationship does not allow the conclusion that changes in the HPA response have a significant impact on the subjective experience of craving. Nevertheless, based on the consistent previous findings that opioid withdrawal is associated with increased stress hormone release [22–24], the elevated ACTH levels might be a possible explanation for the higher subjective craving scores.

The advantages of the present study are its randomized, controlled, crossover design and the adequate sample size, which allowed for the control of confounding variables and sequence effects. On the other hand, the stressful stimuli presented in the fMRI session were not a valid stress test (such as the Trier Social Stress Test [42]). However, performance tasks which could be unfavorably evaluated by others, as used here, constitute psychological stress, and the relevance of such tasks to increased cortisol and ACTH responses has already been shown [43]. Most notably, fMRI scanning has been demonstrated to be a stressful experience associated with elevated cortisol concentrations in healthy persons and depressive patients [44–46]. In substance use disorders, psychosocial stress is generally considered to be a predictive factor for relapse [19, 47, 48].

Several previous studies have established positive effects of DAM maintenance in heroin dependence in patients for whom MMT or abstinence-orientated (drug-free) therapy had been unsuccessful [32, 33, 35–39]. Despite the above-mentioned limitations, the present study supports the efficacy of HAT and provides potential evidence for clinical implications. MMT-resistant patients who seem to react strongly to stress may possibly profit in particular from DAM maintenance. Short-acting opioids (e.g. heroin) seem to lessen the heightened stress reactivity and desire for heroin, as observed in former heroin users without opioid maintenance treatment [25–27], and might thereby prevent relapse with its serious consequences. However, based on the intravenous administration of DAM, there is a greater risk of negative side effects in HAT (respiratory depression, epileptic seizure) [36, 38, 49]. Under medical supervision and with an adequate waiting period after DAM injection, such incidents can be avoided, so that the safety and efficacy of the treatment remain assured. In addition to the injectable form, oral administration as a tablet is possible [50].

HAT is an established treatment form for severe opioid dependence in Switzerland and the Netherlands [32]. For those chronic heroin-dependent patients who initially do not profit from other treatments, it is an effective alternative treatment and complements the therapeutic spectrum for opioid dependence [51]. Moreover, recent research has indicated the efficacy of HAT even in heroin-dependent patients with no previous maintenance experience [52]. A better understanding of the acute effects of DAM (heroin) would therefore promote the optimization of the treatment for chronic opioid dependence.

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Acute Effects of Intravenous Heroin on the Hypothalamic-Pituitary-Adrenal Axis Response

A Controlled Trial

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Abstract: Heroin dependence is associated with a stressful environment and with dysfunction of the hypothalamic-pituitary-adrenal (HPA) axis. The present study examined the acute effects of intravenous heroin versus placebo on the HPA axis response in heroin-dependent patients.

Twenty-eight heroin-dependent patients in heroin-assisted treatment and 20 age- and sex-matched healthy participants were included in a controlled trial in which patients were twice administered heroin or saline in a crossover design, and healthy controls were only administered saline. The HPA axis response was measured by adrenocorticotropic hormone (ACTH) levels and by cortisol levels in serum and saliva before and 20 and 60 minutes after substance administration. Craving, withdrawal, and anxiety levels were measured before and 60 minutes after substance application. Plasma concentrations of heroin and its main metabolites were assessed using high-performance liquid chromatography.

Heroin administration reduces craving, withdrawal, and anxiety levels and leads to significant decreases in ACTH and cortisol concentrations ($P < 0.01$). After heroin administration, cortisol concentrations did not differ from healthy controls, and ACTH levels were significantly lower ($P < 0.01$). In contrast, when patients receive saline, all hormone levels were significantly higher in patients than in healthy controls ($P < 0.01$).

Heroin-dependent patients showed a normalized HPA axis response compared to healthy controls when they receive their regular heroin dose. These findings indicate that regular opioid administration protects addicts from stress and underscore the clinical significance of heroin-assisted treatment for heroin-dependent patients.

Key Words: addiction, cortisol, diacetylmorphine (DAM), heroin-assisted treatment (HAT), heroin dependence, hypothalamic-pituitary-adrenal (HPA) axis

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S ubstance dependence is a chronic relapsing brain disorder that is characterized by an overwhelming compulsion to seek and use drugs, despite negative consequences.[1] It is well known that substance dependence is marked by abnormal hypothalamic-pituitary-adrenal (HPA) axis function.[2,3] An atypical stress response occurs in both heroin and cocaine dependence.[4–6]

Whereas cocaine activates the HPA axis and thus elevates adrenocorticotropic hormone (ACTH) and cortisol levels,[7] heroin and other opiates may suppress stress hormone secretion.[8,9] HPA axis activation has been observed during opioid withdrawal syndromes.[10,11]

Stress and stress response are closely associated with drug use. Stress is known to increase drug craving, anxiety, ACTH, and cortisol secretion and may be associated with further drug use.[12–15]

It has been argued that heroin-dependent patients suffer from persistent hyperresponsiveness to stress, even after detoxification, which reflects heightened sensitivity of the hypothalamus and the pituitary gland to negative emotional stimuli and, consequently, might contribute to later drug use.[16]

Maintenance treatment with methadone or buprenorphine is seen as the treatment of choice in heroin dependence.[17] Alternative pharmacological strategies have been considered as treatment options, including the prescription of heroin [diacetylmorphine (DAM)] itself. Heroin-assisted treatment (HAT) is now available in several countries and has given good outcomes.[18]

Regular opioid administration could damp the inadequate stress response of heroin-dependent patients and thus defend the individual from aversive experiences such as negative affects.[19]

There is empirical evidence that the altered HPA axis function in heroin dependence partially returns to normal during opioid maintenance treatment.[20,21] However, some abnormalities in the HPA axis response seem to persist even during stable opioid maintenance treatment.[22,23] This study examined the acute effects of heroin on the HPA axis response in heroin-dependent patients, in comparison to placebo and to healthy participants. For ethical reasons, healthy controls were included for placebo administration only. We hypothesized that HPA axis activity would be reduced after heroin administration and that the HPA response in heroin-dependent patients would be normalized in comparison to healthy participants.

PATIENTS AND METHODS

Study Sample

Table 1 summarizes the sociodemographic and diagnostic characteristics of the study sample. Twenty-eight heroin-dependent outpatients were recruited from the Division of Substance Use Disorders of the Psychiatric Hospital of the University of Basel (Switzerland). They were aged 23 to 58 years (mean age, 41.3; SD, 6.6), met the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (*DSM-IV*) diagnostic criteria for opioid dependence and had been in HAT for

TABLE 1. Sociodemographic and Diagnostic Characteristics of the Study Sample

	Experimental Group (n = 28)	Control Group (n = 20)	P
Age, mean (SD), y	41.3 (6.6)	40.3 (10.9)	0.718
Male sex, n (%)	19 (67.9)	14 (70.0)	0.875
Partnership, n (%)	9 (32.1)	15 (75.0)	0.003
Employment, n (%)	11 (39.3)	20 (100.0)	<0.001
Disability, n (%)	9 (32.1)	0 (0.0)	0.005
Doses of DAM, mg/d	318.6 (131.7)	—	—
Methadone-equivalent doses, mg/d	79.7 (32.8)	—	—
Duration of heroin dependence, y	20.8 (6.6)	—	—
Age at the first-time heroin use, y	19.0 (3.4)	—	—
Duration of opioid maintenance, y	6.7 (4.5)	—	—
Diagnosis of personality disorder	13 (46.4)	0 (0.0)	<0.001
Substance use			
Tobacco (%)	28 (100.0)	20 (100.0)	1.000
Number of cigarettes/d	21.0 (9.1)	11.5 (8.2)	<0.001
Cocaine (%)	15 (53.6)	0 (0.0)	<0.001
Cannabis (%)	8 (28.6)	5 (25.0)	0.53

6.7 years on average (SD, 4.5). Their daily dose of prescribed heroin ranged from 30 to 700 mg per day.

The inclusion criteria were age older than 18 years, history of intravenous heroin dependence, having been on current stable HAT for at least 6 months, and unchanged heroin dose during the previous 3 months. Exclusion criteria were a positive alcohol breathalyzer test and an additional physical disease or psychiatric disorder, including other comorbid substance dependence.

In the HAT regime, heroin is administered twice a day. The details of the HAT program in Switzerland have been described elsewhere in more detail.[24,25]

When patients fulfilled the inclusion criteria, the history of heroin and other illicit substance use was assessed with the semistructured interview according to the *International Classification of Diseases, 10th Revision* research criteria. Patients were told to abstain from illicit drug use other than prescribed heroin for the duration of the study, from alcohol intake for 72 hours and from tobacco consumption for 2 hours before scanning. Before the experiment, the patients had no opioid intake for approximately 10 hours.

The healthy controls were carefully screened using a semistructured clinical interview to exclude psychiatric or physical illness or a family history of psychiatric illness. Participants who had ever used any other illicit psychotropic drug, who consumed more than 20 g alcohol per day, or who had any psychiatric, neurologic, or severe medical illness history, were also excluded. Healthy controls were recruited from the general population by advertisement in the same geographical area. After the study had been completely described to the subjects, written informed consent was obtained. The study was approved by the local ethics committee.

Study Design

The heroin-dependent patients were examined on 2 occasions 1 week apart, in a crossover design. The patients were randomly assigned after simple randomization procedures (computerized random numbers) to 1 of 2 injected substance (heroin vs placebo = saline). One patient group (n = 14) received first heroin before the experiment, whereas the second patient group (n = 14) received first saline. One week later, they received the other substance before the experiment. All patients were informed that they received heroin or placebo before or after the experiment. The patients and the experimenter were blind to the administered substances. The healthy controls participated only in the placebo condition. The study has been registered by the Web site http://clinicaltrials.gov (IDNCT01174927).

Study Procedure

The study procedure is shown in Table 2. At the start of the study day, a urine sample was collected for screening for amphetamines, benzodiazepines, cocaine, methamphetamine, morphine, and cannabis using immunometric assay kits. Alcohol use was tested with an alcohol breathalyzer test.

After completion of the baseline measurement, heroin-dependent patients received either their dose of prescribed heroin in 5 mL or the same dose of saline, through an indwelling intravenous catheter during period of 30 seconds. Healthy controls were injected with 5 mL of saline over 30 seconds. Heroin was provided by the Swiss Federal Office of Public Health in

TABLE 2. Study Procedure

7:00 A.M.	Entry in the laboratory. Screening for adherence to study protocol, medical screening, Tox-urine tests, alcohol breathalyzer tests
7:15 A.M.	Baseline assessment before substance application
7:30 A.M.	Placement of intravenous catheter, baseline heroin plasma samples, baseline hormone samples (ACTH plasma, cortisol serum, cortisol saliva)
1. Substance injection	Intravenous heroin or saline administration
+ 3 min	Heroin plasma samples
+ 10 min	Heroin plasma samples
+ 20 min	Hormone samples (ACTH plasma, cortisol serum, cortisol saliva)
+ 60 min	Heroin plasma samples, hormone samples (ACTH plasma, cortisol serum, cortisol saliva)
9.00 A.M.	Second assessment after substance application
2. Substance injection	Intravenous saline or heroin administration
9.30 A.M.	End of the experiment

the form of the hydrochloride salt. It was dissolved in sterile water on site and aspirated into a syringe, adapted to the evacuated infusion system.[26]

Adrenocorticotropic hormone and cortisol were taken as measures of the HPA axis response. Samples were collected through an intravenous catheter at baseline, 20 and 60 minutes after substance administration. The concentrations of heroin and its metabolites were obtained at baseline and 3, 10, and 60 minutes after the patients had received their heroin injection. Self-report measures were assessed before and 60 minutes after substance application.

Bioanalytical and Biochemical Measurements

The concentrations of DAM and its metabolites were measured in venous ammonium-heparinized plasma obtained from 23 patients at baseline and 3, 10, and 60 minutes after individualized heroin injection. Plasma levels of DAM, 6-acetylmorphine (6AM), morphine (M), morphine-3-β-D-glucuronide (M3G), and morphine-6-β-D-glucuronide (M6G) were assessed using high-performance liquid chromatography on a 125 × 2 mm i.d. Nucleosil 50 C-8 ec column with a particle size of 5 μm and a 8 × 3-mm i.d. precolumn packed with Nucleosil 120 C-8 and a particle size of 3 μm, followed by diode-array detection. Sample preparation and instrumental conditions were as described previously in detail.[27] Minor optimization steps included the adjustment of the sample pH to 8.0 for the solid-phase extraction, to prevent DAM hydrolysis, and the multistep gradient applied during the chromatographic separation.

Salivary cortisol was analyzed with a time-resolved immunoassay with fluorescence detection, as described elsewhere.[8] Total cortisol concentrations were measured in serum with the Immulite 2000 Cortisol-Test (Siemens, Germany). The measurement range of the test is at 1 to 50 μg/dL; the analytical sensitivity is 0.20 μg/dL. The test shows an intraassay precision of 7.4% and an interassay precision of 9.4%. The reference range of the concentration of cortisol depends on the time of day, with morning levels of 5 to 25 μg/dL. ACTH was measured in EDTA plasma with the ACTH Immulite-Test (Siemens). The intraassay precision was less than 6.1% for concentrations greater than 50 pg/mL; the interassay precision was 9.4% for concentrations greater than 51 pg/mL. The analytical sensitivity of this test is 9 pg/mL. The recovery range of this test is 91% to 107%. The median of a study with 59 test persons in good health (male/female) performed by the manufacturer showed a value of 24 pg/mL and a 95%-reference range of n.d. to 46 pg/mL.

Interviews and Self-Report Measures

Clinically experienced psychiatrists conducted the Structured Clinical Interview for *DSM-IV* for *DSM-IV* Axis II Disorders (SCID-II)[28] to assess the diagnosis of a comorbid personality disorder. The Heroin Craving Questionnaire was assessed to measure perceived craving and withdrawal level.[29,30] The State-Trait Anxiety Inventory was administered to examine the state anxiety.[31]

Statistical Analyses

Statistical analyses were conducted using SPSS for Windows (version 17.0). Primary end points were the cortisol and ACTH levels.

A repeated-measures analysis of variance (ANOVA) was performed with the 2 within factors for substance (heroin vs saline) and 3 time points (baseline, 20, and 60 minutes after substance injection). The factor order of the substance was randomized between subjects. The random order of substance administration, age, sex, and personality disorder diagnosis were used as covariates. When within factors were significant, Tukey post hoc tests were performed. To protect against violations of sphericity, repeated-measures data were adjusted for within-factor degrees of freedom, using the Greenhouse-Geisser correction where appropriate.

The differences between heroin-dependent patients and healthy controls were tested with *t* test for the 3 primary end points. Because of multiple comparisons, α was adjusted for 7 tests using the Bonferroni correction. As consequence, all statistical tests were considered significant at a 2-tailed level of $P < 0.0072$.

RESULTS

Plasma Concentrations of Heroin and Its Metabolites

Heroin (DAM) peak plasma concentrations rose to 1005 ng/mL at 3 minutes after heroin administration, due to the extremely short plasma elimination half-life of the drug. At the last sampling time point, DAM (35–139 ng/mL) was still measurable in 3 patients. 6AM exhibited a similar time-concentration profile to that of DAM. M was detectable in all patients and at all sampling time points after administration of DAM, with a peak plasma concentration at 3 minutes (20 patients) and 10 minutes (3 patients). The decline in the plasma concentrations of M was considerably slower than for DAM and 6AM, reflecting the much longer elimination half-life for M compared to the acetylated compounds. At 3, 10, and 60 minutes, the concentration ranges were 39 to 3885, 31 to 761, and 29 to 436 ng/mL, respectively. This indicates relatively stable plasma levels of M during prolonged period, with the highest interindividual variability observed at 3 minutes. The M3G and M6G plasma concentrations steadily increased over the study period of 60 minutes, approaching a plateau at the end of the study. At the last sampling time point, the M3G concentrations were between 281 and 4432 ng/mL. Considerably lower concentrations were found for M6G, ranging between of 81 and 1099 ng/mL. The plasma profiles of heroin and its metabolites are depicted in Figure 1.

Effects of Heroin on Self-Report Measures

After the application of heroin, perceived craving (t = 5.19, *df* = 27, $P < 0.001$) and withdrawal (t = 4.42, *df* = 27, $P < 0.001$) decreased significantly. After saline injection, the withdrawal level increased significantly (t = −2.83, *df* = 27, $P < 0.01$) and craving scores did not change. The state anxiety decreased after heroin administration (t = 6.16, *df* = 27, $P < 0.001$), and did not change after saline. After heroin administration, patients did not differ from healthy controls in their self-report measures.

Effects of Heroin Versus Saline in Heroin-Dependent Patients

The repeated-measures ANOVA showed a significant substance (heroin vs saline) and time interaction for ACTH (F = 11.21, $P = 0.001$), serum cortisol (F = 45.59, $P < 0.001$) and saliva cortisol concentrations (F = 20.16, $P < 0.001$) in heroin-dependent patients ($P < 0.001$). Moreover, there were significant time effects for ACTH (F = 6.06, $P = 0.014$) and serum cortisol levels (F = 16.46, $P < 0.001$).

According to the post hoc tests, ACTH decreased significantly from baseline to 20 minutes (F = 5.54, $P < 0.05$) and from 20 to 60 minutes after heroin administration (F = 40.65, $P < 0.0001$). Serum cortisol (F = 51.50, $P < 0.0001$) and saliva cortisol (F = 12.99, $P = 0.001$) decreased from baseline to 20 minutes after heroin administration, and serum cortisol (F = 42.50,
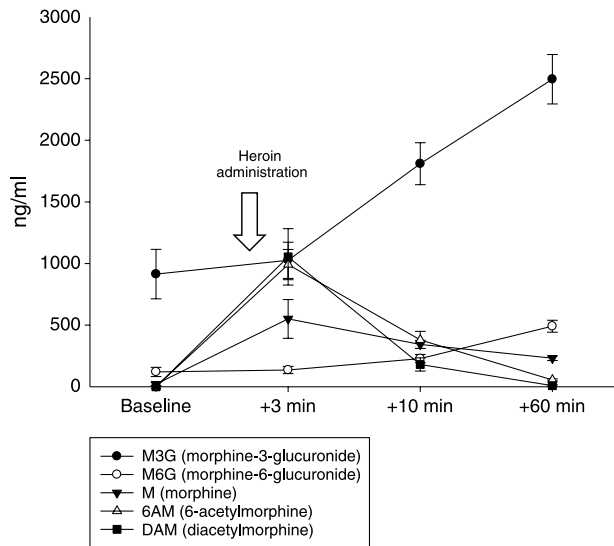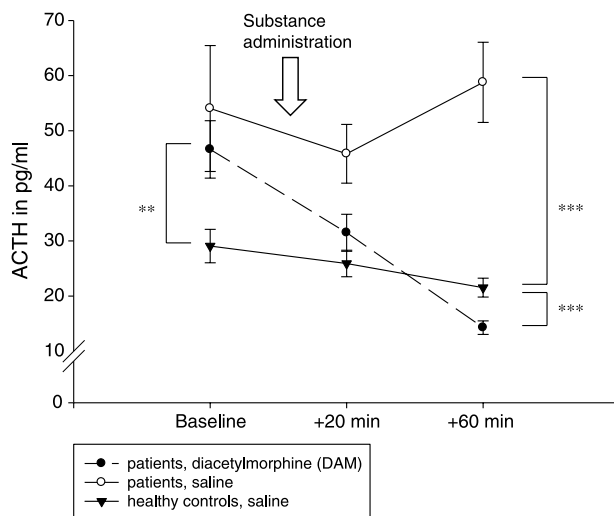
FIGURE 1. Plasma concentrations of heroin (DAM) and its main metabolites in heroin-dependent patients before and after heroin injection. Means and standard errors are displayed.
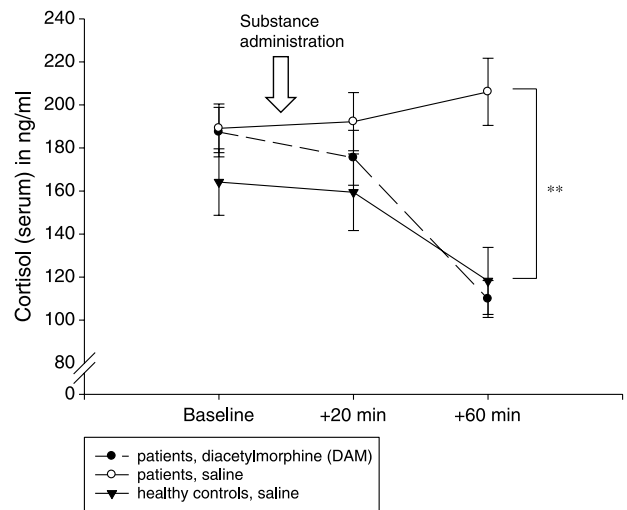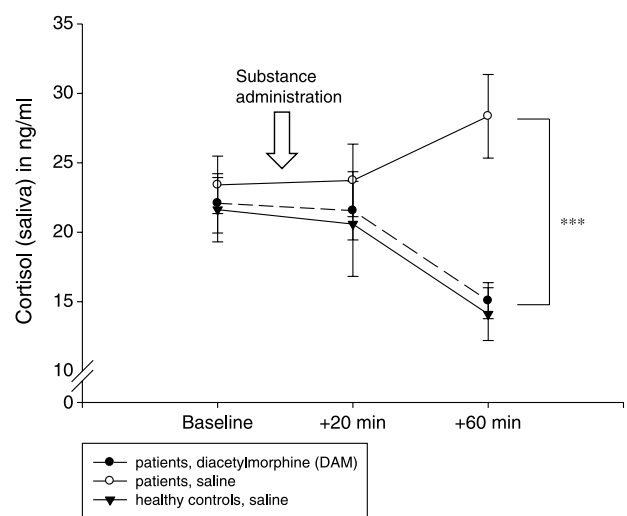

FIGURE 3. Serum cortisol concentration in heroin-dependent patients before and after heroin or saline injection and healthy controls after saline injection. Means and standard errors are displayed. **$P < 0.01$.

$P < 0.0001$) and saliva cortisol (F = 26.70, $P < 0.0001$) decreased again from 20 to 60 minutes after heroin administration. We included random order of substance administration, age, sex, and personality disorder diagnosis as covariates in the ANOVA. There was no significant influence on stress hormone levels.

Effects of Heroin and Saline in Heroin-Dependent Patients Versus Saline in Healthy Controls

The differences in stress hormone levels between heroin-dependent patients and healthy controls during the experiment are shown in Figures 2–4. At baseline, ACTH concentrations were significantly higher in patients than in healthy controls (t = 2.96, df = 37.52, $P = 0.005$). Sixty minutes after substance administration, serum cortisol and salivary cortisol did not

differ between heroin-dependent patients and healthy controls when patients received heroin. ACTH concentrations were significantly lower 60 minutes after heroin administration in heroin-dependent patients than in healthy controls (t = −3.55, df = 46, $P = 0.001$). When the heroin-dependent patients received saline, ACTH (t = 4.98, df = 29.97, $P < 0.0001$), serum cortisol (t = 3.87, df = 46, $P < 0.0001$), and salivary cortisol concentrations (t = 4.01, df = 43.17, $P < 0.0001$) were significantly higher than in healthy controls at the end of the experiment.

DISCUSSION

This study examined the acute effects of heroin on the HPA axis response in heroin-dependent patients compared to placebo and to healthy controls. We found that all stress hormones decreased in heroin-dependent patients after heroin administration.

FIGURE 2. ACTH concentration in heroin-dependent patients before and after heroin or saline injection and healthy controls after saline injection. Means and standard errors are displayed. **$P < 0.01$, ***$P < 0.001$.

FIGURE 4. Saliva cortisol concentration in heroin-dependent patients before and after heroin or saline injection and healthy controls after saline injection. Means and standard errors are displayed. ***$P < 0.001$.

Importantly, stress hormone levels did not differ (cortisol) or were even lower (ACTH) than those in healthy controls when they received heroin. However, during saline treatment, the stress hormone levels were higher in patients than in healthy controls. This finding highlights the acute suppressive effect of heroin on the HPA axis. Moreover, it indicates that—even on stable opioid maintenance treatment—heroin-dependent patients still show a different HPA axis response than healthy persons when they do not receive their daily opioid dosage. We have found a higher HPA axis response in heroin-dependent patients after saline injection than in healthy control persons. This finding supports previous results showing partial normalized HPA axis activity in methadone-maintained heroin-dependent patients compared to active and former heroin users.[16] It could be inferred that heroin-dependent patients in HAT need to inject their daily heroin dose to suppress their HPA axis activity.

Before substance administration, hormone levels (ACTH) were elevated in patients compared to controls. This probably reflects the beginnings of withdrawal symptoms, given that the dose of heroin had not yet been administered. After heroin administration, but not after placebo, we found the expected decrease in patients' craving and withdrawal level.

The observed plasma concentrations of heroin and its metabolites confirmed the very short half-life of heroin and revealed a plateau phase, with relatively stable plasma levels of the active metabolite morphine during prolonged period after 10 minutes, underscoring this acute stress suppressive effect of heroin, even 1 hour after administration.[32]

The clinical consequences of this heroin effect on the HPA axis have not been clear. However, it has been suggested that—in contrast to increased dopamine and opioid peptide function—increased corticotropin-releasing factor and cortisol levels are associated with negative effects and stress like-states in drug users.[33] Additionally, animal models have shown that acute stress induces drug-seeking behavior and drug self-administration after prolonged abstinence, indicating the significance of stress-like states for craving and relapse.[34] In animals, this stress-induced reinforcement of drug-seeking behavior seems to depend particularly on the activation of CRH levels and the extended amygdale.[35] In heroin-dependent patients, the activation of the amygdala is followed by a decrease in the activation of different brain areas, including the amygdala, after methadone[36] and buprenorphine administration.[37]

We demonstrated a decrease in negative affects such as anxiety after heroin administration. This dampening effect of negative affects—including craving and withdrawal level—highlights the acute emotional regulation effect of heroin administration and may be a relevant factor in maintaining drug-taking behavior.[38] Previous studies have demonstrated the emotional regulation effect of methadone application too, but with slightly higher opioid doses.[8] Moreover, studies on intravenously injected heroin may better reflect the pattern of drug use in heroin addicts.

Our findings suggest that heroin and other opioids may contribute to the normalization of impaired emotional processing and emphasize the benefits of regular opioid substitution for heroin-dependent patients.[39]

We conclude that HPA axis activity and negative affects can be significantly suppressed by regular opioid administration in heroin-dependent patients, which may also prevent later illegal drug use and relapse.

Our patients were recruited from a population which mainly consisted of individuals with long-standing polysubstance use. Although this problem is virtually inevitable when chronic heroin-dependent individuals are examined, it may have biased the results. The findings may thus not apply to all groups of heroin users and maintenance patients. We examined the effects of heroin in a controlled study design that is only possible in a country that has HAT programs. We did not have a completely balanced study design. However, there was no significant influence of the random order of the injected substance in the patient group.

These limitations notwithstanding, we think our results retain significant clinical implications. They establish that heroin suppresses the HPA axis response and may protect stress-sensitive heroin-dependent patients against their heightened stress response.

AUTHOR DISCLOSURE INFORMATION

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Acute Effects of Heroin on Emotions in Heroin-Dependent Patients

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Background: Euphoria has been described in heroin-dependent individuals after heroin administration. However, affective disturbances and disorders are common in heroin dependence. The present study examined the acute effects of heroin on emotions in heroin-dependent patients.
Methods: This randomized controlled crossover trial included 28 heroin-dependent patients (67.9% male, $n = 19$) in stable heroin-assisted treatment and 20 healthy controls. The patients were administered heroin or saline (placebo), the controls were administered saline. Data measuring mood, affects and heroin craving (BDI, AMRS, STAI, STAXI, and HCQ) were assessed before and 60 minutes after substance injection.
Results: Before substance injection, heroin-dependent patients showed significantly higher levels of anxiety and depression than healthy controls ($p < .0001$). Heroin administration—but not placebo administration—was associated with a significant decrease in all negative emotions, including craving, and a significant increase in emotional well-being ($p < .0001$), irrespective of perceived intoxication and sedation. After the experiment, the patients did not differ from healthy controls in their emotions, once they had received heroin.
Conclusions: Heroin dampens craving, negative emotions, and increases positive emotions. These findings indicate that heroin regulates emotions and underscore the clinical benefit of opioid substitution treatment for heroin-dependent patients. (Am J Addict 2013;XX:1–7)

INTRODUCTION

Heroin dependence is a chronically relapsing disorder that has been characterized by a compulsion to seek and use heroin despite negative consequences.[1,2] After detoxification, a high percentage of heroin-dependent patients suffer a relapse into daily drug use.[3] In heroin-dependent patients, there is a frequent comorbidity with psychiatric disorders. In 47–97% of these patients, psychiatric comorbidities have been found.[4] In particular, affective disorders have been frequently described in heroin addicts.[5–7] Studies have indicated that individuals who regularly use heroin are at high risk for elevated levels of anxiety and anxiety linked disorders.[8,9] These studies suggest an association between anxiety-related processes and regular heroin use, although no data is available on the process that may underlie such a linkage. There are multiple reasons to expect an association between anxiety sensitivity, which is defined as the fear of anxiety-related sensations, and chronic heroin use.[10] It has generally been found that individuals with high levels of anxiety tend to use psychoactive substances.[11–14] High levels of anxiety and stress have been found to be associated with drug craving and drug use.[15,16] In heroin-dependent patients, heroin craving was most robustly associated with increases in sadness and anger.[17]

Thus, there seems to be a direct connection between heroin craving and negative emotions in heroin dependence which can be suppressed directly after heroin use.

Clinical observations have identified many emotion-related signs in the development and maintenance of drug addiction. It has been argued that the escape and avoidance of negative affects—manifested as specific emotion such as anxiety, irritability, or sadness—are a key motive for further addictive drug use.[18,19] The negative emotion is the motivational core of the withdrawal syndrome. Due to the repeated cycles of drug use and withdrawal, substance-dependent individuals learn to identify interoceptive cues of negative affect preconsciously. Hence, the motives for further substance use are not under cognitive control.[18] Galynker et al.[20] presume that, even in the absence of comorbid affective disorders, heroin-dependent patients may have a lasting vulnerability to emotional dysregulation.

It has been demonstrated that maintenance treatment with opioid agonists produces favorable treatment maintenance

in heroin dependence.[21] Opioid substitution treatment for heroin dependence relieves heroin withdrawal, and curbs heroin craving.[22] This holds true for opioid substitution with methadone or buprenorphine, as well as for heroin-assisted treatment (HAT) with diacetylmorphine (pharmaceutical heroin, DAM), which have shown satisfactory outcomes.[23–26]

However, the acute effects of heroin on subjective negative and positive emotions have not been investigated in a randomized controlled trial with stable opioid-maintained patients. We hypothesized higher levels of negative emotions, such as depressiveness, anxiety, and anger in heroin-dependent patients, compared to healthy controls at baseline. We expected normalization of emotions in heroin-dependent patients given heroin, compared to controls. We also anticipated no change in negative emotions after administration of placebo.

PATIENTS AND METHODS

Study Sample

Twenty-eight patients (67.9% male, $n = 19$) were recruited from the Division of Substance Use Disorders of the Psychiatric Hospital of the University of Basel (Switzerland). They were aged 23–58 years (average age = 41.3, SD = 6.6), met the DSM-IV diagnostic criteria for opioid dependence and had been in heroin-assisted treatment (HAT) for 6.7 years on average (SD = 4.5).

All participants were native German speakers. The last administration of their half-daily dose of heroin before the examination had taken place during the afternoon of the previous day. Participants were told to abstain from illicit drug use other than prescribed heroin for the duration of the study, from alcohol intake for 72 hours, and from tobacco consumption for 2 hours before scanning. All participants were cigarette smokers.

Inclusion criteria were: age older than 18 years, history of intravenous heroin dependence, being on current HAT for at least 6 months, and unchanged dose conditions during the previous 3 months. Exclusion criteria were a positive alcohol breathalyzer test and an additional physical disease or psychiatric disorder, including other comorbid substance dependence except tobacco. Patients with cocaine and cannabis abuse who did not fulfill the criteria of substance dependence were not excluded.

The history of heroin and other illicit substance use was assessed with the semi-structured interview according to ICD-10 research criteria. All patients had had at least two in-patient detoxification treatments for heroin dependence, established opioid substitution, and had participated in the standardized HAT program (JANUS, University of Basel, Switzerland).

This includes the prescription of pharmaceutical DAM and psychosocial treatment and is established in several countries for severe heroin dependence.

The healthy controls were carefully screened, using a semi-structured clinical interview to exclude psychiatric or physical illness or a family history of psychiatric illness. Controls were also excluded who had ever used any other illicit psychotropic drug, who consumed more than 20 g alcohol/day, or who had any psychiatric, neurologic, or severe medical illness history. Controls were recruited from the general population by advertisement in the same geographical area. They were informed that the aim of the study was to investigate the acute effects of heroin on emotions in heroin-dependent patients. They were included as healthy controls, receiving a neutral substance (saline).

After the study had been fully described to the subjects, written informed consent was obtained. The study was approved by the local ethics committee.

TABLE 1. Socio-demographic and diagnostic characteristics of the study sample

Measurements	Mean (SD)		p-Value
	Experimental group (n = 28)	Healthy controls (n = 20)	
Age	41.3 (6.6)	40.3 (10.9)	.718
Male gender (%)	19 (67.9)	14 (70.0)	.875
Partnership (%)	9 (32.1)	15 (75.0)	.003
Employment (%)	11 (39.3)	20 (100.0)	.000
Doses of heroin (mg/day)	318.6 (131.7)	—	
Duration of dependence (years)	20.8 (6.6)	—	
Age at first heroin use (years)	19.0 (3.4)	—	
Duration of opioid maintenance (years)	6.7 (4.5)	—	
Substance use			
Tobacco (%)	28 (100.0)	20 (100.0)	1.000
Number of cigarettes/day	21.0 (9.1)	11.5 (8.2)	<.001
Cocaine (%)	15 (53.6)	0 (.0)	<.001
Cannabis (%)	8 (28.6)	5 (25.0)	.53

SD = standard deviation.

Table 1 gives an overview of the diagnostic and socio-demographic characteristics of the study sample.

Procedure

The present study is a randomized placebo-controlled crossover clinical trial. This study has been registered by the website http://clinicaltrials.gov (ID NCT01174927). Heroin-dependent patients were informed that they would receive their half-daily dose of heroin or placebo before or after the experiment. Allocation to both groups was randomized. One week later, the patients completed the other condition with the opposite sequence of substance administration. Healthy controls only participated in the placebo-session. After completion of the baseline data assessment and urine drug testing, heroin-dependent patients administered their regular half-daily heroin dose (mean 319 mg/day = 80 mg metha-done equivalent) or the same amount of liquid of saline through an indwelling intravenous catheter over a period of 30 seconds. Healthy controls were injected 5 ml of saline. Heroin (diacetylmorphine) was provided by the Swiss Federal Office of Public Health in the form of hydrochloride salt. It was dissolved in sterile water on site and aspirated into a syringe, adapted to the evacuated infusion system. This administration procedure is described in detail by Stohler et al.[27] The patients and the experimenter were blind to the administered substance. Five minutes after substance injection, patients reported their "rush" and their withdrawal level on visual analog scales (VAS). Sixty minutes after substance injection, patients filled out VAS for intoxication and sedation level and a second data assessment to measure their emotional state.

Data Assessments

The Heroin Craving Questionnaire (HCQ)[28] was used to measure heroin craving. A reliability of $\alpha = .94$ was calculated. The corresponding scale contains nine items and measures the desire to use heroin. The Beck Depression Inventory (BDI), a 21-question multiple-choice self-report inventory, was used to assess the depressiveness, with a score above 14 indicating mild depression.[29] The state-trait anxiety inventory (STAI) was administered; this includes two well validated 20-item scales, with separate measures of state and trait anxiety.[30] The author notes that state anxiety may fluctuate over time and can vary in intensity. Trait anxiety indicates relatively stable individual anxiety proneness, and refers to a general tendency to respond with anxiety to perceived threats in the environment. The state-trait anger expression inventory-2 (STAXI)[31] was used to assess anger. The 57-item inventory measures the intensity of anger as an emotional state (State Anger) and the disposition to experience angry feelings as a personality trait (Trait Anger). The 60-item Likert-scale short version of the adjective mood rating scale (AMRS)[32] was used to assess emotional excitation and well-being as two emotional domains of the AMRS. Good validity and reliability have consistently been demonstrated for all questionnaires.

Data Analysis

Statistical analyses were conducted using SPSS for Windows (version 19). Descriptive data were analyzed by means of unpaired t-tests for continuous variables or χ^2 tests for discrete variables, where appropriate. Group differences in trait variables at baseline (depression score, trait anxiety, trait anger) were examined using one-way analysis of variance (ANOVA) with three group levels (heroin, placebo, and controls). State variables were analyzed by repeated-measures ANOVA with two time points (baseline and 60 minutes later), with within-subjects or group factors (heroin, placebo, and controls) and between-subjects factor. The intoxication and sedation level were used as covariates. The order of the substance administration was randomized between subjects. To protect against violations of sphericity, repeated-measures data were adjusted for within-factor degrees of freedom using Huynh–Feldt corrections, where appropriate. Where the within-subject factor was significant, post hoc planned t-tests comparisons were performed to identify significant differences. All statistical tests were considered significant at a two-tailed level of $p < .05$.

RESULTS

Affects and Mood at Baseline

Before substance administration, at baseline, heroin-dependent patients exhibited significantly higher depression scores than the healthy controls ($t = -7.10$, df = 46, $p < .0001$), with an average score of 14, and higher trait anxiety ($t = -5.75$, df = 46, $p < .0001$). The trait anger level did not differ significantly between the groups.

Drug Effects, Withdrawal Symptoms, and Heroin Craving

Significantly more drug effects and fewer withdrawal symptoms were reported immediately after heroin injection than after placebo ($p < .0001$). Only one placebo effect was observed, as one patient rated saline as heroin. After placebo injection, heroin craving did not change over time. After heroin administration, craving decreased significantly ($t = 5.19$, df = 27, $p < .0001$). Compared to placebo, significantly lower craving was reported at the end of the experiment when patients received heroin ($t = -5.63$, df = 27, $p < .0001$).

Effects of Heroin on State Anxiety

Repeated-measures ANOVA showed a significant time effect [$F = 13.06$, $p = .001$], a significant group effect [$F = 14.71$, $p = <.0001$], and most importantly, a significant interaction effect [$F = 5.18$, $p = .008$] for state anxiety. There was no effect of subjective intoxication or sedation. As shown in Table 2, state anxiety decreased after heroin administration [$t = 6.16$, df = 27, $p < .0001$], but not after placebo. After heroin administration, patients did not differ from healthy controls at the end of the experiment. After

TABLE 2. Mood and affects of the study sample

Measurements	Mean (SD)			p-Value group differences
	Experimental group with heroin (n = 28)	Experimental group with placebo (n = 28)	Controls with placebo (n = 20)	
State anxiety				
Before substance application	41.9 (10.0)	43.7 (8.9)	31.7 (4.6)	
60 min after substance application	35.11 (7.4) ***	42.3 (9.3)	30.6 (5.4)	Pat + placebo vs. Controls: ***
State anger				
Before substance application	12.0 (2.6)	11.3 (2.2)	10.1 (0.3)	
60 min after substance application	10.3 (1.0) ***	12.9 (4.0) *	10.3 (1.1)	Pat + placebo vs. Controls: **
Emotional excitation				
Before substance application	19.2 (5.8)	18.9 (5.7)	14.3 (2.3)	
60 min after substance application	15.3 (3.3) ***	21.9 (6.8) ***	13.7 (2.8)	Pat + placebo vs. Controls: ***
Well-being				
Before substance application	15.8 (4.0)	15.8 (3.8)	20.6 (5.2)	
60 min after substance application	18.4 (3.9) ***	15.1 (3.8)	20.5 (4.1)	Pat + placebo vs. Controls: ***

SD = standard deviation; *$p < .05$; **$p < .01$; ***$p < .001$.

placebo administration, heroin-dependent patients also had a higher anxiety level than healthy controls [$t = 5.06$, df = 45, $p < .0001$].

Effects of Heroin on State Anger

According to the ANOVA, state anger showed a significant group effect [$F = 14.71$, $p = <.0001$], and a significant interaction effect [$F = 5.18$, $p = .008$]. The intoxication and sedation level had no significant influence. After the administration of heroin, anger decreased significantly [$t = 6.16$, df = 27, $p < .0001$], whereas it increased after placebo administration [$t = -2.11$, df = 27, $p = .044$]. Table 2 shows that after placebo the patients had significantly higher anger levels than healthy controls [$t = 2.83$, df = 46, $p = .007$].

Effects of Heroin on Emotional Excitation

There was a significant group effect [$F = 11.70$, $p = <.0001$], and a significant interaction effect [$F = 21.98$, $p < .0001$] for emotional excitation. The covariates intoxication and sedation had no significant effect. After heroin, but not after placebo, the emotional excitation level decreased significantly [$t = 4.62$, df = 27, $p < .0001$] and no longer differed from healthy controls (Table 2).

Effects of Heroin on Well-being

ANOVA showed a significant group effect [$F = 13.03$, $p = <.0001$] and a significant interaction effect [$F = 4.20$, $p = .019$] for well-being. There was no significant influence of the covariates intoxication and sedation. The well-being levels increased significantly after heroin administration [$t = -3.58$, df = 27, $p = .001$]. The patients rated their well-being higher after heroin than after placebo [$t = 3.31$, df = 27, $p = .002$]. After heroin administration, well-being reached the level of healthy controls (Table 2).

DISCUSSION

To our knowledge, this is the first study to examine the acute effects of heroin on emotions in heroin-dependent patients compared to placebo and healthy controls.

We found that all negative emotions—including heroin craving—decreased, whereas well-being increased after heroin administration to heroin-dependent patients; this was irrespective of their perceived intoxication and sedation level. When they had received heroin, the emotions of the heroin-dependent patient no longer differed from those of healthy controls. The negative emotions were higher when they

received saline. These findings may highlight the acute emotional regulation effect of heroin in stable opioid-maintained heroin-dependent patients.

The role of heroin as an emotional modulator has been discussed in the development and maintenance of drug addiction. Our findings were consistent with previous studies, showing a higher level of anxiety and depressive features in heroin addicts compared to healthy controls, and possibly indicating affective vulnerability.[18,19] This vulnerability could be associated with less tolerance and ability to cope with emotional stress. Therefore heroin may be needed as auxiliary support, as our results show alignment of emotions to the healthy controls.

It has been found that current opioid users without any withdrawal symptoms had a higher emotional response to unpleasant emotional stimuli images than healthy participants and lower response to pleasant images than abstinent former users.[33] Moreover, using functional imaging, heroin addicts showed a greater neural response to negative emotional stimuli than to positive stimuli, whereas healthy controls showed the opposite pattern.[19] In other psychiatric illnesses associated with disturbed affective regulation, for example, depression and borderline personality disorder, the endogenous opioid system involved in representation and regulation of emotion showed modified responses to emotional challenges.[34,35]

The neurophysiological effects of opiates in human brains have been studied thoroughly. It is known that opioids—such as diacetylmorphine—unfold their effects on different opioid-receptors, the μ-receptor being assumed to play an important role in addiction.[36] Broad expression of μ-opioid receptors is found in brain areas involved in the initiation and maintenance of drug dependence. In the early stage of drug (ab)use the reward system is activated (nucleus accumbens, ventral tegmental area), whereas continued substance abuse leads to dysregulation of the reward system.[37] Other brain circuits involved in the stress-system and the obsessive-compulsive system then become more active (amygdala, hippocampus, anterior cingulate, prefrontal cortex), resulting in altered emotional states and processing, recurring craving for the substance and failed impulse suppression.[36,38]

The use of opioids leads to physiological symptoms (analgesia, sedation, hypothermia, miosis), as well as to subjective perceived effects.[39,40] Kosel et al.[39] described a short rush-sensation immediately after intravenous heroin administration and a period of euphoria after 15 minutes. Our findings show higher negative emotions before substance administration and normalization following the drug administration and are in line with these previous studies on neurobiological concepts of addiction.

On the assumption that there is altered processing of affective stimuli and evoked emotional response in opioid users, heroin could be effective in correcting emotional dysregulation, and attenuating unpleasant affective states, as our findings showed that administration of heroin dampens negative emotions, including craving. The use of heroin could be considered as a kind of self-medication to balance the affective homeostasis and constitutional or acquired emotional vulnerability of the addicted brain.[41] It has been shown that acute administration of opioids suppresses cortisol levels and leads to a reduction in craving in heroin-dependent patients.[42,43] Moreover, the first neuroimaging studies investigating the acute effects of oral opioid administration on brain function showed reduced activity in limbic brain areas during drug-related cues following methadone[44] and buprenorphine administration[45] indicating emotional regulation from regular opioid substitution. In our study, after heroin administration, the emotional states of heroin-dependent patients aligned with those of healthy controls.

Other psychotropic substances also show significant effects on emotional modulation. The reduction in negative affects (eg, stress, tension, anxiety) is a known acute effect of alcohol consumption.[46–49] It appears that the emotional imbalance of heroin addicts is even more severe than in addicts to other substances which dampen negative emotions and that heroin addicts have an even greater need to suppress negative emotions. Moreover, many heroin addicts live in a stressful environment under adverse circumstances (eg, homelessness, prostitution, illegality/delinquency, social isolation), with constant exposure to negative stimuli in the course of increasing drug use.[50] This ongoing stressor may therefore sustain the desire for repeated drug use.

The pattern of heroin use is characterized by recurrent craving for the substance. It has been found that the increase in negative affects, such as sadness and anger, was significantly associated with drug craving.[17] Therefore it is possible that a reduction in heroin craving is associated with a reduction in negative emotions. However, this association does not demonstrate causality.

Generally, drug addiction shows attributes of both impulsive (rapid and unplanned action regardless of the consequences) and compulsive behavior (perseveration despite negative outcome).[1] The development of the addiction has been seen as a progression from impulsivity to compulsivity.[51] During this process, the motivational drive changes. Whereas the early impulsive drug use is positively reinforced by generating pleasant effects, the ongoing substance use is characterized by the intention to eliminate negative emotions and unpleasant craving, negative reinforcement being the driving force of this vicious circle. The findings of our study on stable opioid-maintained heroin-addicted patients with a long history of drug use, suggest that dampening of negative emotions is a relevant factor for maintaining the drug use in an advanced stage of the addiction.

We did not observe opioid withdrawal symptoms during the experiment. Moreover, withdrawal symptoms were generally not expected at a methadone equivalent dosage of over 25 mg/day.[52] Our patients were in stable HAT and were informed that they would receive their regular half-daily heroin (40 mg methadone equivalent dose on average) at the latest 60 minutes after the first substance injection.

Our findings are limited by the moderate sample size and the varying doses of administered heroin. However, the

individually prescribed half-daily heroin doses were established during the heroin-assisted treatment, on the basis of the patient's personal needs and had not been changed before the study. Due to the cross-over design of the study, patients knew the sequence of the administered substance when attending the second session of the experiment, and were therefore unblinded. However, in our experimental study we were able to examine the acute effect of heroin administration on emotions in a controlled setting, whereas previous studies were often based on retrospective assessments under less controlled conditions, for example, unknown substances in street heroin.

Our patients were recruited from a population which mainly consisted of individuals with long-standing polysubstance use. Although this problem is virtually inevitable when chronic heroin-dependent individuals are examined, it may have biased the results. The findings may thus not apply to all groups of heroin users and maintenance patients.

These limitations notwithstanding, we think our results retain significant clinical implications. This article could serve as an up-to-date confirmation of a widely observed clinical phenomenon. Heroin-dependent patients have higher levels of negative emotions in the absence of the drug. We could demonstrate the positive effect on emotional regulation, even 1 hour after heroin administration. Acute heroin administration dampens craving and negative emotions and leads to normalization of the impaired emotions in heroin-dependent patients. Our findings emphasize the benefits of opioid maintenance treatment for heroin-dependent patients.

Declaration of Interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper.

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