Acute Effects of Heroin on Negative Emotional Processing: Relation of Amygdala Activity and Stress-Related Responses

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Background: Negative emotional states and abnormal stress reactivity are central components in drug addiction. The brain stress system in the amygdala is thought to play a key role in the maintenance of drug dependence through negative reinforcement. Although acute heroin administration was found to reduce anxiety, craving, and stress hormone release, whether these effects are reflected in amygdala activity has not yet been investigated.

Methods: With a randomized, crossover, double-blind design, saline and heroin were administered to 22 heroin-dependent patients, whereas 17 healthy control subjects were included for the placebo administration only. We used functional magnetic resonance imaging to investigate blood oxygen level–dependent responses during fearful faces processing. Stress reactivity was measured by adrenocorticotropic hormone levels and by cortisol concentrations in serum and saliva 60 min after substance administration. Anxiety and craving levels were assessed with self-report ratings.

Results: Heroin administration acutely reduced the left amygdala response to fearful faces relative to the saline injection. Patients receiving saline showed a significantly higher left amygdala response to fearful faces than healthy control subjects, whose activity did not differ from patients receiving heroin. The left amygdala activity correlated significantly with scores on state-anxiety and levels of adrenocorticotropic hormone, serum cortisol, and saliva cortisol among all patients and control subjects.

Conclusions: Our results show a direct relation between the acute heroin effects on stress-related emotions, stress reactivity, and left amygdala response to negative facial expressions. These findings provide new insights into the mechanisms underlying negative reinforcement in heroin addiction and the effects of regular heroin substitution.

Key Words: Acute heroin administration, amygdala, anxiety, fearful face processing, fMRI, stress hormones

Acute withdrawal in drug addiction is accompanied by negative affects characterized by dysphoria, irritability, anxiety, as well as abnormal stress reactivity that drives drug seeking through negative reinforcement mechanisms (1). Activation of brain stress systems is hypothesized to be a key element of the negative emotional state produced by dependence (2,3), and previous models of negative reinforcement emphasize the pivotal role of negative affect in motivating sustained drug use (4). It has been shown that abstinent heroin-dependent individuals reveal elevated stress reactivity, which could be related to heightened craving and symptoms of withdrawal (5). Indeed, hypothalamic-pituitary-adrenal (HPA) axis activation has been reported during opioid withdrawal syndromes (6), whereas opioid agonists are associated with a reduction in stress hormone secretion (7). Our group previously found suppressed cortisol concentrations (5) and reduced craving scores after acute methadone administration in heroin-dependent patients (6). Moreover, we recently demonstrated a normalized HPA axis response measured by adrenocorticotropic hormone (ACTH) and cortisol concentrations as well as a decrease in negative emotions such as anxiety and craving compared with healthy control subjects (HC) when heroin-dependent patients received their regular dose of heroin (8,9). This dampening effect of negative emotions highlights the emotional regulation effect of acute heroin administration and helps to understand how drug taking is maintained through negative reinforcement. However, the neural correlates of these effects have not yet been investigated.

Emotional processing including the recognition of the feelings of other people from their facial expression is fundamental to social interaction and behavior (10). Abstinent heroin abusers especially demonstrate an exaggerated number perception of negative expressions and an understated number perception of positive expressions when compared with neutral schematic expressions (11). When compared with HC, abstinent heroin abusers exhibit a significantly heightened number perception of negative expressions (12), suggesting a negative emotional face processing bias in heroin-dependent subjects during states of withdrawal and craving. Emotional faces, especially negative expressions increase neuronal activity relative to neutral faces in specific brain areas, including the left amygdala (13,14), whereas its volume is positively correlated with that of social networks (15). Studies have consistently reported a direct relation between left amygdala response to fearful faces and state-anxiety [for a review see Calder *et al.* (16)]. Accordingly, the negative emotional processing bias in depressed individuals is characterized by left amygdala hyperactivity in response to fearful faces (17). Furthermore, all components of the corticotropin releasing factor system are expressed in the amygdala (18) and compulsive drug use

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associated with dependence is mediated by recruitment of brain stress systems in the extended amygdala (2).

In the current study, we provide a framework for studying negative reinforcement mechanisms in heroin addiction by exploring how the negative emotional feelings during withdrawal might motivate renewed drug intake by linking neuronal, physiological, and subjective responses. In particular, we measured the acute effects of controlled doses of heroin on neuronal activity in response to fearful faces in heroin-dependent patients relative to an injection of saline (experimentally induced state of withdrawal) as well as compared with HC by using functional magnetic resonance imaging (fMRI). We specifically focused on the amygdala as a region of interest, given the crucial role of the amygdala during fearful face processing (19). Furthermore, we investigated whether the amygdala activity was related to scores of subjects on anxiety, ACTH, and cortisol level as well as to heroin craving in patients. The results on stress hormones have already been published (8). We use them here to explore the relation to the amygdala activity. We expected, on the basis of the recently reported acute heroin-induced decrease of anxiety and stress hormone release (8,9) and of previous evidence revealing a key role of the amygdala in opioid-reinforcement mechanisms (20), that acute heroin administration would reduce the amygdala response to fearful faces in heroin-dependent patients.

Methods and Materials

Patients

The study was approved by the local ethics committee and registered with ClinicalTrials.gov (see registry information after acknowledgments). After receiving a written and oral description of the aim of this study, all participants gave written informed consent statements before inclusion.

Twenty-two patients with opioid dependence according to ICD-10 criteria were recruited from the Centre of Substance Use Disorders of the University Hospital of Psychiatry in Basel. The included patients were older than 18 years and had a past history of intravenous heroin consumption with a current heroin-assisted treatment for at least 6 months with an unchanged heroin dose during the previous 3 months. Patients received no additional medication besides their individualized dose of heroin. Patients with a positive alcohol breathalyzer-test, additional physical disease, or psychiatric disorder including other comorbid conditions like substance dependencies were excluded from participation. Clinically experienced psychiatrists conducted a structured clinical Interview for DSM-IV Axis II Disorders to assess the diagnosis of comorbid personality disorders.

Healthy control subjects ($n = 17$) were carefully screened, with a semi-structured clinical interview to exclude psychiatric or physical illness or a family history of psychiatric illness. Control subjects were also excluded who consumed more than 20 g alcohol/day or who had any psychiatric, neurologic, or severe medical illness history. The Barratt Impulsiveness Scale was used to assess trait measure of impulsivity in both groups (21). Control subjects 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 face recognition in heroin-dependent patients. They only received saline.

Control subjects and patients were told to abstain from illicit drug consumption for the duration of the study as well as to abstain from alcohol intake and smoking 72 and 2 hours before scanning, respectively. Nevertheless, 4 HC and 7 patients tested positive for cannabis, and 9 patients tested positive for cocaine at one or both points of the measurement. Characteristics of subjects are summarized in Table 1.

Experimental Design

Saline and heroin were administered through an indwelling intravenous catheter over a period of 30 sec, with a cross-over, double-blind, vehicle-controlled design. Heroin hydrochloride was dissolved on site in 5 mL of sterile water and aspirated into a syringe as previously described (22). Each patient was scanned twice, with a short interval between scans (mean 9 $\pm$ 3.8 days). Subjects who received their individualized dose of heroin before the first scanning session received 5 mL of saline before the second session, and vice versa. Of the 22 included patients, 11 received heroin at the first scan and saline at the second, whereas in the 11 patients, the sequence was reversed. Furthermore, in both sessions all heroin-dependent patients received both heroin and saline. That is, the subjects who received heroin before scanning were administered vehicle after scanning (i.e., 60 min after the first injection), whereas the subjects who received saline before scanning were administered heroin after scanning. The HC participated only in the placebo condition.

Craving ("desire to use heroin") was assessed 60 min after saline/heroin treatment with the 45-item Heroin Craving Questionnaire (23), which measures positive and negative aspects of craving on five theory-derived nine-item scales. The German version of the State-Trait Anxiety Inventory was used to quantify state-anxiety after both treatments in patients as well as in HC (24).

The results on stress hormones have already been published (8). Because we adapted this data to the patients included in the

Table 1. Characteristics of Participants

	Healthy Control Subjects ($n = 17$)	Heroin Dependents ($n = 22$)	Statistics
Age, yrs (SD)	42.24 (2.58)	41.05 (7.21)	$F = .173$; $p = .68$
Gender (women/men)	4/13	8/14	$\chi^2 = .742$; $p = .49$
Education, yrs (SD)	14.65 (.62)	10 (2.67)	$F = 29.95$; $p < .001$
Employment (yes/no)	17/0	9/13	$\chi^2 = 15.068$; $p < .001$
Barratt Impulsiveness Scale (SD)	69.65 (6.21)	67.32 (6.51)	$F = .93$; $p = .341$
Number of Cigarettes/Day (SD)	10.35 (8.37)	20.09 (8.84)	$F = 12.18$; $p < .01$
Cannabis Consumption, *n* (%)	4 (24)	7 (32)	$\chi^2 = .325$; $p = .725$
Cocaine Consumption, *n* (%)	0	9 (41)	$\chi^2 = 9.041$; $p < .005$
Age at First-Time Heroin Use, yrs (SD)	—	19.09 (3.27)	—
Duration of Dependence, yrs (SD)	—	21 (6.40)	—
Daily Heroin Dose, mg (SD)	—	309.55 (121.48)	—