



Cerebral blood flow effects of acute intravenous heroin administration

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Abstract

We examined acute effects of intravenous diacetylmorphine (heroin) administration – which induces a characteristic biphasic response: A short rush-sensation associated with intense pleasurable feelings followed by a subjectively different period of euphoria on cerebral blood flow. This was assessed in nine male heroin dependent patients participating in a heroin maintenance program in a setting resembling everyday pattern of heroin abuse. ^{99m}Tc-HMPAO was administered 45 s (rush) and 15 min (euphoria) after administration of i.v. heroin and 45 s after administration of saline (placebo). Plasma concentration of diacetylmorphine and its metabolites were measured with high-pressure liquid chromatography (HPLC). Compared to the euphoria condition, rush was associated with blood flow increase in the left posterior cerebellar lobe, left anterior cingulate gyrus and right precuneus. Our results are in line with recent reports indicating that the cerebellum is an important component in functional brain systems subserving sensory and motor integration, learning, modulation of affect, motivation and social behaviour, which all play important roles in reinforcing properties of opioids.

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1. Introduction

Drug addiction remains a major concern of public health, direct and indirect costs of heroin addiction exceed those

engendered by most of the other illicit drug dependencies (Bammer et al., 1999) (Brown, 2004). Better knowledge on the neurobiology of drug addiction might lead to improved therapeutic strategies, functional neuroimaging allowed steps towards this goal. Compared to stimulating drugs or alcohol, opioids and especially diacetylmorphine received little attention (Gatley et al., 2005; Lingford-Hughes, 2005; Lingford-Hughes et al., 2003). In states of acute opioid administration effects on regional cerebral blood flow (rCBF) have been studied in healthy volunteers with a history of substance abuse, nondependent opioid abusers, methadone-substituted opioid abusers and sporadic opioid abusers (London et al., 1990; Walsh et al., 1994; Firestone et al., 1996; Schlaepfer et al., 1998; Sell et al., 1997, 1999). Research protocols vary widely, relatively low numbers of subjects were included and results are inhomogeneous. To our knowledge, no functional neuroimaging studies assessing realistic drug abuse patterns of heroin addicts are available. Effects on rCBF have however been studied in conditions such as abstinence (Gerra et al., 1998), withdrawal and craving (Daglish et al., 2001; Danos et al., 1998; Krystal et al., 1995; Rose et al., 1996) or opioid maintenance therapy (Krystal et al., 1995; Pezawas et al., 2002).

Opioids induce a wide range of physiological symptoms (analgesia, drowsiness, respiratory depression, pupillary constriction) and subjective effects (euphoria, relaxation, excitement, and pleasure) (Gutstein and Akil, 2005). Subjective effects of diacetylmorphine are characteristic and consist of a biphasic effect: The first phase, which starts almost immediately after intravenous injection of diacetylmorphine and lasts for several minutes, is characterized by a rush-sensation which is associated with a warm flushing of the skin and a state characterized by a feeling of having no worries. This is followed by a period of tranquil high, euphoria, that lasts for up to 1 h (Seecof and Tennant, 1986). Since rush is not experienced with a slower onset of opioid action (oral or subcutaneous routes), addicts may persist in intravenous use despite its risks (Jaffe et al., 1997). However, literature is scarce concerning subjective effects of diacetylmorphine taken habitually and in high doses as in long-term heroin addicts (Tschacher et al., 2003).

Diacetylmorphine has a very short half-life in the circulation, due to rapid conversion to 6-acetylmorphine and morphine by esterases present in the blood, the liver and the brain and to rapid distribution. Both, 6-acetylmorphine and morphine are glucuronated in the liver. These hydrophilic metabolites are subsequently excreted in urine. Diacetylmorphine passes the blood-brain barrier rapidly resulting in almost instant pharmacodynamic effects. It is likely that μ -receptors in the brain mediate effects of euphoria. Therefore, as binding to μ -receptors requires a free phenolic hydroxyl (3-OH) group in the morphinan structure, diacetylmorphine seems not to bind to these receptors actually acting as a pro-drug for 6-acetylmorphine. 6-acetylmorphine and morphine can be considered active metabolites. Arterial peak plasma concentrations of diacetylmorphine and 6-acetylmorphine result after 1.1–2.8 min and after 0.7–2.7 min. These are associated with the mentioned rush effect. Both substances are hydrolyzed rapidly, resulting in short half-lives, 1.3–3.8 min for diacetylmorphine and 9.3–49 min for 6-acetylmorphine. Morphine peak concentrations generally occur after 3.6–

7.8 min and it is detectable in plasma for much longer (half-life 109–287 min). The same is true for the active conjugate, morphine-6-glucuronide (T_{max} 1 h, half-life 4 h) (Klous et al., 2005; Rentsch et al., 2001; Seecof and Tennant, 1986).

We studied immediate and delayed pharmacokinetic and pharmacodynamic effects of intravenous diacetylmorphine administration in a male population of chronic drug abusers. Using HMPAO-SPECT we investigated the effects on rCBF during both the rush- and the euphoria-phases in a partially blinded, balanced, placebo-controlled design and we measured the concentrations of diacetylmorphine and its metabolites in venous blood at various time points.

2. Experimental procedures

This study was approved by the Institutional Review Board of the Medical Faculty of the University of Bern and the National Review Board of the Swiss PROVE study (controlled diacetylmorphine maintenance therapy) (Bammer et al., 1999; Brehmer and Iten, 2001; Steffen et al., 1999). Subjects provided written informed consent.

Ten right-handed, male opioid addicts (mean age $\pm$ standard deviation (SD): 32.9 $\pm$ 5.1 years) who were enrolled in the Swiss diacetylmorphine prescription program (PROVE) participated in this study. They were all diagnosed with opioid dependence according to the Diagnostic & Statistical Manual of the American Psychiatric Association (DSM IV, American Psychiatric Association, 1994). Concomitant medical and psychiatric disorders were assessed by review of the medical documentation of the PROVE program and in a psychiatric interview. One of the subjects had an HIV-A2 status without any symptoms of acquired immunodeficiency syndrome (AIDS) and one had a diagnosis of comorbid alcohol dependence according to the documentation of the PROVE program. This subject was not excluded from the participation in the study, since at baseline; neither the psychiatric interview nor the laboratory tests indicated current alcohol dependence. All of the subjects consumed cannabis, and four flunitrazepam, on a regular basis. Study participants had abused opioids for 14.3 $\pm$ 5.7 years. One reached as highest educational level elementary school, three secondary school and 5 completed an apprenticeship. Exclusion criteria were clinically significant medical comorbidity, comorbid psychiatric axis one diagnosis according to DSM IV, as well as the use of other addictive substances excepted nicotine, cannabis, alcohol and benzodiazepines (as mentioned, controlled for with urine drug screening tests). The study participants consumed a mean daily dose of 462 $\pm$ 129.4 mg diacetylmorphine distributed in two or three intravenous injections. None of the subjects showed clinically pathological results in routine laboratory blood analysis (haematology, liver and kidney parameters).

Subjects were examined on three days, at the same time of the day (start of the protocol between noon and 13:00), 48 h apart. Three conditions (rush, euphoria and placebo) were studied in a randomized, partially blinded balanced design. The analysis of imaging data was done blinded to the experimental condition; patients were partially blinded since they were in all cases able to correctly guess which substance was administered due to their extensive knowledge of the characteristic effects of diacetylmorphine. On two days (rush and euphoria), diacetylmorphine doses, which were 20% higher than one third of the usual daily dose, were administered in order to obtain a robust drug effect. On one study day, normal saline was injected (placebo). At the beginning of every study session, all subjects were asked whether they were in a state of craving. This was not the case at any occasion.

In every condition, approximately 20 mCi of the SPECT blood flow tracer [^{99m}Tc]-HMPAO was injected intravenously using the same catheter system which was used to inject the diacetylmorphine or saline containing solutions. In the rush-condition the tracer was

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