Pattern of regional cerebral blood-flow changes induced by acute heroin administration - a perfusion MRI study

Modèle de variations du flux sanguin cérébral régional induit par l’administration aiguë d’héroïne - une étude en IRM de perfusion

S. Guyer\(^a,b\), M. Kosel\(^c\), S. Altrichter\(^d\), M. El-Koussy\(^b\), R. Haemmig\(^f\), H.-U. Fisch\(^a\), K.-O. Lovblad\(^b,d,*\), T.E. Schlaepfer\(^a,c,e,f\)

\(^a\) Psychiatric Neuroimaging Group, Department of Psychiatry, University Hospital, Bern, Switzerland
\(^b\) Division of Neuroimaging, Department of Radiology, University Hospital, Bern, Switzerland
\(^c\) Brain Stimulation Group, Department of Psychiatry, University Hospital, Bonn, Germany
\(^d\) Department of Radiology, Geneva University Hospital, 24, rue Micheli-du-Crest, 1211 Geneva 14, Switzerland
\(^e\) Division of Psychiatric Neuroimaging, Department of Psychiatry, The Johns Hopkins Medical Institutions, Baltimore, MD, USA
\(^f\) Department of Psychiatry, University of Bern, Switzerland

Available online 19 November 2007

KEYWORDS

Addiction; Brain imaging; Perfusion MRI

Abstract

Purpose. — Although both the subjective and physiological effects of abused psychotropic substances have been characterized, less is known about their effects on brain function. We examined the actions of intravenous diacetylmorphine (heroin), the most widely abused opioid, on regional cerebral blood flow (rCBF), as assessed by perfusion-weighted MR imaging (PWI) in a double-blind and placebo-controlled setting.

Material and Methods. — Eight male subjects dependent of diacetylmorphine (mean age 36 years, range: 26 to 44 years), who had participated in a clinical diacetylmorphine maintenance program, underwent PWI with gadolinium injection. At two sessions separated by 2-7 days, the participants were examined 80 s after intravenous administration of either diacetylmorphine or saline. rCBF in four regions of interest (amygdala, vermis of the cerebellum, anterior cingulated cortex and thalamus) was compared with heroin versus placebo.

Results. — In the cerebellum, thalamus and cingulated cortex, there were no significant differences in perfusion values between diacetylmorphine and placebo. In the amygdala, perfusion values were 0.8 ± 0.4 and 0.5 ± 0.2 on the left, and 0.9 ± 0.4 and 0.6 ± 0.3 on the right,
with diacetylmorphine and with placebo, respectively (t-test results were $P = 0.044$ and $P = 0.033$ on the left and right sides, respectively). Other differences in perfusion values between the drug and placebo did not reach statistical significance.

Conclusion. — Perfusion MRI demonstrated differences in brain hemodynamics induced by drug intake.

© 2007 Elsevier Masson SAS. All rights reserved.

Résumé

Objectif. — Bien que les effets subjectifs et physiologiques de l’abus de substances psychotropes aient été bien caractérisés, leur effet sur le fonctionnement cérébral est moins connu. Nous avons étudié l’effet de l’administration intraveineuse de diacétylmorphine (hééroïne) sur le débit sanguin cérébral régional (DSCR) par IRM de perfusion au cours d’une étude randomisée en double insu contre placebo.

Matériel et méthode. — Huit sujets dépendant à l’héroïne ont été inclus et explorés par IRM de perfusion avec injection de gadolinium. Au cours de deux sessions séparées de deux à sept jours d’intervalle, les participants étaient explorés 80 secondes après injection soit d’héroïne soit d’un placebo. Le DSCR, mesuré dans quatre régions d’intérêt (amygdale, vermis cérébellux, cingulum antérieur et thalamus), était comparé entre les conditions héroïne ou placebo.

Résultats. — Il n’y avait pas de différence significative des valeurs de perfusion dans le cervelet, le thalamus et le cortex cingulaire. Dans l’amygdale, les valeurs de perfusion étaient $0.8 \pm 0.4$ et $0.5 \pm 0.2$ du côté gauche et $0.9 \pm 0.4$ et $0.6 \pm 0.3$ du côté droit dans les conditions respectivement héroïne et placebo (t-test à $p = 0.044$ du côté gauche et 0,033 du côté droit). Les autres différences des valeurs de perfusion entre les groupes héroïne et placebo n’étaient pas significatives.

Conclusion. — L’IRM de perfusion permet de mesurer des altérations hémodynamiques cérébrales induites par les substances psychotropes.

© 2007 Elsevier Masson SAS. All rights reserved.

Introduction

Drug addiction remains a major concern in public health, and comes with tremendous direct and indirect costs. Costs engendered by diacetylmorphine (heroin) dependence and its related risks, such as infection with the human immunodeficiency virus (HIV) or viral hepatitis, and social costs due to associated crime and poverty exceed those of most other abused drugs [1,2].

A better understanding of the mechanisms of drug addiction might result in improved therapeutic strategies [17]. An essential method in clinical research is functional neuroimaging. In recent years, this has allowed a significant increase in knowledge of the neurobiology of addiction [4,12]. However, unlike psychostimulants and alcohol, opioids and, specifically, diacetylmorphine have received little scientific attention, with the result that only a few brain-imaging studies assessing its effects have been published so far [8,19].

Important advances have been made during the last decade in perfusion-weighted MRI (PWI) techniques that allow measurement of hemodynamics parameters [21] and assessment of brain-perfusion abnormalities in different pathological conditions and, especially, in stroke and brain tumors [3,10]. The effects of opioids on regional cerebral blood flow (rCBF) have been studied in states of acute intoxication in healthy volunteers who have a history of substance abuse using intramuscular administration of morphine [20], intramuscular administration of hydromorphone and butorphanol in non-dependent opioid abusers [26], methadone-substituted opioid abusers with intravenous administration of diacetylmorphine [25], sporadic opioid abusers with intramuscular injection of buprenorphine [32] and in healthy volunteers with intravenous administration of fentanyl [7]. Unfortunately, as the research protocols varied widely and relatively low numbers of subjects were involved, it is not surprising that the results are somewhat mixed. In addition to the studies already mentioned, effects on rCBF have been studied in conditions such as drug abstinence [9], withdrawal and craving [4,5,18,23], and opioid maintenance therapy [18,22]. However, to our best knowledge, no perfusion MRI studies have been done to investigate the acute effects of diacetylmorphine in dependent patients in a setting resembling conditions of common drug addiction.

Opioids induce a wide range of physiological symptoms, including analgesia, drowsiness, respiratory depression and pupillary constriction, as well as subjective effects such as euphoria, relaxation, excitement and pleasure [11]. The subjective pharmacodynamic effects of diacetylmorphine typically consist of a well-described 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 associated with warm flushing of the skin and a feeling of having no worries. This brief rush phase is followed by a tranquil ‘high’ phase, euphoria, lasting for up to one hour [27]. As the subjective effect of the rush is generally not experi-
enced with a slower onset of opioid action, such as when administered by oral or subcutaneous routes, addicts usually persist in abusing drugs intravenously despite the considerable risks involved [13, 14]. In general, there is little data on behavioral and experiential effects of diacetylmorphine taken habitually and in high doses [30].

In this study, we assessed the immediate pharmacodynamic effects of diacetylmorphine administered intravenously in men who are chronic heroin addicts. We used a perfusion MRI protocol to investigate the effects on rCBF during the rush phases according to a double-blind, crossover, placebo-controlled design. We investigated cerebral blood-flow changes in regions of interest—specifically, the thalamus, amygdala, anterior cingulate cortex and superior part of the cerebellar vermis. We anticipated changes in regional cerebral blood flow based on published data.

Materials and methods

This study was conducted according to the Declaration of Helsinki [31] and approved by the local institutional review board at the University of Bern. Written informed consent was obtained from all study participants. Eight right-handed male opioid addicts (mean age: 36.0 years; range: 26-44 years) who were enrolled in the Swiss heroin prescription program (PROVE) [29] participated in the study. In this program, substitution doses were adapted individually and administered two or three times a day (mean substitution dose/day: 401 mg; range: 140-600 mg). Study participants all tested negative for HIV, and hepatitis B and C, and were all diagnosed as being opioid-dependent according to the Diagnostic and Statistical Manual of Mental Disorders (DSM IV) by the American Psychiatric Association [6]. Concomitant medical and psychiatric disorders were assessed by review of the medical documentation generated by the PROVE program and an additional psychiatric interview. The participants’ clinical characteristics are listed in Table 1. Exclusion criteria were clinically significant medical comorbidity, comorbid psychiatric axis 1 diagnosis according to DSM IV [6], contraindications for undergoing MRI and concomitant use of other addictive substances except for nicotine, cannabis, alcohol or benzodiazepines, controlled for by urine drug-screening tests. The subjects were paid for study participation a sum equivalent to US$140.00.

Investigations were conducted in two sessions, 2-7 days apart. At the beginning of the sessions, all subjects had mild-to-moderate symptoms of opiate craving such as sweating or restlessness. In a double-blind setting, diacetylmorphine or a placebo (saline) was substituted at the usual time of heroin administration. The dose of heroin was 20% higher than the usual injected dose to maximize drug effects.

To assess the effects of opioids on pupil diameter, we measured the area of the pupils 27 ± 9 and 30 ± 8 mins before, and 15 ± 4 and 14 ± 3 mins after, the injection of heroin and placebo, respectively [16]. Blood oxygenation levels and heart rates were recorded automatically every 5 seconds. We compared total counts of oxygenation levels (as a percentage of maximum saturation) and pulse rate (heartbeats/min) recorded for 4 min approximately 15 mins before, and for 4 mins approximately 15 mins after, administration of either the diacetylmorphine or saline.

MRI studies of the brain were performed using a 1.5-Tesla Magnetom Vision MRI Scanner (Siemens Medical Systems, Erlangen, Germany), with a head coil, capable of echoplanar imaging (EPI) techniques—specifically, diffusion-weighted MRI (DWI) and PWI. In addition, we acquired thin sagittal 3-D T1-weighted MRI sections for normalization in the scanning probe microscopy (SPM) analysis. Each patient was scanned on different days after receiving either heroin or placebo under double-blind and randomized conditions. In each case, we acquired DWI and PWI scans in corresponding slice positions to allow tissue parameter correlation. The perfusion scans were obtained exactly 80 seconds after intravenous administration of heroin or placebo to the subject while in the scanner itself, followed by the DWI. Isotropic single-shot, spin-echo, echoplanar DWI (TR/TE: 5100/137 ms; 240 mm; matrix: 96*128; NEX: 4) gener-

Table 1 Clinical characteristics of the subjects

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Weight (kg)</th>
<th>Comorbidity</th>
<th>Heroin intake (mg)</th>
<th>Other substance-abuse</th>
<th>Craving</th>
<th>Mean pulse rate before/after heroin or placebo intake (beats/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Morning Noon Evening Total Day 1 Day 2 Day 1 Day 2</td>
</tr>
<tr>
<td>1</td>
<td>39</td>
<td>M</td>
<td>65</td>
<td>Diabetes mellitus</td>
<td>200</td>
<td>200 200 600</td>
<td>Alcohol</td>
<td>Moderate Severe</td>
</tr>
<tr>
<td>2</td>
<td>26</td>
<td>M</td>
<td>82</td>
<td>None</td>
<td>60</td>
<td>None 80 140</td>
<td>None</td>
<td>Mild Mild</td>
</tr>
<tr>
<td>3</td>
<td>44</td>
<td>M</td>
<td>80</td>
<td>None</td>
<td>300</td>
<td>None 300 600</td>
<td>Alcohol</td>
<td>Moderate Mild</td>
</tr>
<tr>
<td>4</td>
<td>41</td>
<td>M</td>
<td>80</td>
<td>None</td>
<td>120</td>
<td>None 120 240</td>
<td>None</td>
<td>Severe Mild</td>
</tr>
<tr>
<td>5</td>
<td>33</td>
<td>M</td>
<td>78</td>
<td>None, benzodiazepine</td>
<td>150</td>
<td>150 150 450</td>
<td>Alcohol,</td>
<td>Moderate Mild</td>
</tr>
<tr>
<td>6</td>
<td>31</td>
<td>M</td>
<td>70</td>
<td>None</td>
<td>200</td>
<td>None 300 500</td>
<td>None</td>
<td>Severe</td>
</tr>
<tr>
<td>7</td>
<td>38</td>
<td>M</td>
<td>71</td>
<td>None</td>
<td>120</td>
<td>80 80 280</td>
<td>Alcohol</td>
<td>Moderate Mild</td>
</tr>
<tr>
<td>8</td>
<td>29</td>
<td>M</td>
<td>73</td>
<td>None</td>
<td>80</td>
<td>100 120 300</td>
<td>Alcohol</td>
<td>Mild</td>
</tr>
</tbody>
</table>
ated 20 axial sections (slice thickness, 5 mm; interslice gap, 1.5 mm; total acquisition time, 20 s) with b values of 0.500 and 1000 s/mm². For the PWI, dynamic post-contrast T2*-perfusion gradient-echo EPI images were acquired (TR/TE: 2000/60.7 ms). Twelve axial sections (slice thickness: 5 mm; interslice gap: 1.5 mm; FOV: 240 mm; matrix size: 96 × 128) were imaged 40 times every 2 s, with a total imaging time of 80 s. For obtaining the slices in the PWI scan, we centered them on the DWI slice block. We also injected into the cubital vein, via a wide-bore cannula, a double dose of 0.2 mmol/kg of gadopentate dimeglumine contrast medium (Gadovist; Schering, Berlin, Germany).

Image analysis

Using the PWI series already described, the time shift of intensity of MR signal in each point of the image was assessed using parameters that were calculated directly from the signal curve (MSR: maximum relative reduction of signal). For reduction of the differences in signal intensity, we had previously obtained a time-point normalization value. These data were used to generate parametric images showing the gray scale of each point at the time of arrival (TA) and the time to peak (TP) of the contrast agent (Gadovist). Because of blood-flow variations compared with normal systemic circulation, the time coordinates were not treated as absolute values. Indeed, these varied according to the individual patient but, nevertheless, corresponded to the phenomenon we were examining.

In addition to the phenomenological parameters, several other parameters were calculated, according to the work of Rosen et al. [24], including the relative cerebral blood volume (rCBV; integral under the transformed curve), relative cerebral blood flow (rCBF), mean transit time (MTT) and vascular transit time (VTT) [15]. For these, the global variable (gv) function was alternated to the transformed signal intensity and the analysis of the area under the curve (AUC) for the first moment of the curve. Because of recirculation of contrast, it was necessary to give a time break-off point.

Using the parameter images, an ROI analysis was made in the thalamus, amygdala, cingulate cortex and superior part of cerebellar vermis on each side of the cerebrum and after intravenous heroin or placebo administration. For each anatomical region, we generated the two conditions (heroin and placebo) for rCBF comparison.

Diffusion images showed no changes before and after injection, and the apparent diffusion coefficient (ADC) values also revealed no changes.

Results

Our analyses of the effects of intravenous administration of diacetylmorphine on rCBF in the selected four regions of interest yielded the following results: in the left and right thalami, cerebellum and anterior cingulate cortex (Figs. 1–4), no statistically significant differences were found between placebo and diacetylmorphine. In the vermis, values were 0.8 ± 0.2 and 0.6 ± 0.1 and, in the right amygdala, 0.9 ± 0.4 and 0.6 ± 0.3, with diacetylmorphine and with placebo, respectively. These values were significantly different for diacetylmorphine compared with placebo using two-tailed, paired t testing (P = 0.044 and P = 0.033 on the left and right, respectively). However, left- and right-side differences were not statistically significant (P < 0.05) using unpaired, two-tailed t testing (Fig. 5). These results are shown in Table 2.

On comparing the effects of diacetylmorphine and placebo on pupil diameter, we found a significant reduction in pupil size 15 mins after diacetylmorphine administration.
demonstrating the pharmacodynamics of opioids. At that time, the pupillary surface was 13 ± 7 mm² compared with 27 ± 5 mm² 27 mins before diacetylmorphine injection (paired one-sided t-test, \( P = 0.002 \)). With placebo, the values before injection were not statistically significantly different.

Blood oxygenation levels and pulse rates were also not significantly different during the 4 mins before and after the diacetylmorphine and saline injections, and did not change with drug compared with placebo administration.

Discussion

We looked at the acute effects on rCBF 80 s after intravenous administration of diacetylmorphine, as measured by perfusion MRI in eight diacetylmorphine-dependent men, in a crossover placebo-controlled, double-blind study. Functional neuroimaging results were analyzed using an ROI approach. Our analyses yielded statistically significant increases of rCBF in both sides of the amygdala after diacetylmorphine administration compared with placebo. We
also measured heart rate, arterial blood pressure and the area of the pupils before and after intravenous administration of saline (placebo) and diacetylmorphine. We found a statistically significant difference in pupil area before and after diacetylmorphine, and in comparison to placebo. This finding was as expected and confirms the pharmacodynamic effect of diacetylmorphine.

Our main finding was the increase in rCBF in the amygdala with the drug compared with placebo. This is in line with the results of a previous study in which the acute effects of the prototypical μ-opioid receptor agonist hydromorphone and the mixed agonist/antagonist butorphanol (which has κ-receptor agonist activity) were compared with saline (placebo), using 99mTc-hexamethylpropyleneamine oxime single photon emission computed tomography (HMPAO-SPECT) 60 mins after injection of the studied substance. Subjective effects of the drugs were distinctly different. Hydromorphone pro-

Figure 4  MR perfusion findings with calculation of CBV, MTT, CBF, TA, MTT and VTT parameters in the cerebellum of 8 volunteers after heroin administration.

Figure 5  SPM map showing activation in the right mesial temporal lobe.
Reduced more ratings of “good effects”, whereas butorphanol led to more “bad effects”. Hydromorphone also significantly increased rCBF in the anterior cingulate cortex, amygdala and thalamus—all structures belonging to the limbic system. Butorphanol brought about a less clear-cut picture of regional CBF increases, mainly in the area of both temporal lobes [26].

In our present study, we used DWI to exclude ischemic effects induced by hemodynamic changes after heroin administration. This revealed that the changes are transient and correspond simply to alterations in hemodynamics, and do not lead to irreversible tissue changes. Indeed, DWI is a powerful tool for the detection of such changes.

However, comparing our present results with those of earlier studies is difficult as the applied study protocols, methods of neuroimaging, study populations, opioids used, injected dosages and/or mode of administration vary greatly among the available studies. Also, only one study assessed the acute effects of intravenous heroin administration on regional cerebral blood flow [29]. In this case, H215O–positron emission tomography (PET) data were acquired in 10 methadone patients about 4 mins after intravenous injection of 20 mg of diacetylmorphine or on presentation of visual cues related to drug addiction. The brain regions in which increased activity was recorded included parts of the midbrain, specifically, an area centered on the periaqueductal gray matter, and extending to the ventral tegmental area and dorsal raphe. Only after presentation of the visual cues were additional foci found in the left insula and both cerebellar hemispheres.

In other studies, there was a decrease in brain metabolism after opioid administration. Four opioid addicts receiving regular prescriptions for diacetylmorphine underwent functional magnetic resonance imaging (fMRI) using a visual-activation paradigm before and after intravenous administration of 30 mg of diacetylmorphine. All patients showed a decrease of 37–100% in the extent of activation in the visual cortex in response to visual stimulation between 1 and 44 mins later [28].

In a study of 12 multiple-drug abusers, intramuscular injections of morphine reduced the global cerebral metabolic rate (CMR) and regional CMR in six cortical areas (superior middle and frontal gyri, postcentral gyrus, anterior cingulate gyrus, paracentral lobule and gyrus rectus), around 45 mins after drug administration, as measured by FDG-PET. Irrespective of administration of morphine, a left-greater-than-right asymmetry occurred in the temporal cortex, and an interaction between hemisphere and drug was noted in the postcentral gyrus. In most cases, glucose utilization effects were not significantly related to subjective measures of euphoria [20].

In another study, 21 opioid-dependent subjects abusing diacetylmorphine, or who were in a methadone or morphine maintenance program, and 36 healthy controls were investigated using 99mTc-HMPAO-SPECT. In this case, long-term opioid dependence resulted, in particular, in a decrease in prefrontal cerebral blood flow. A right-greater-than-left asymmetry seen in the healthy controls was reversed in the addicts [22].

To summarize the results of functional imaging studies of the acute effects of intravenous or intramuscular administration of opioids in humans, we conclude that: (a) there are few studies available; (b) study designs vary considerably; and c) the results are generally inconsistent. However, changes of rCBF—whether increases or decreases—are most consistently found in structures of the limbic system.

In the present study, we intended to assess the effects of intravenous diacetylmorphine administration in a setting as close as possible to real-life scenarios for opioid-dependent addicts. We therefore chose to study patients with a diagnosis of chronic diacetylmorphine dependence participating in a diacetylmorphine-substitution program. We administered 20%-higher diacetylmorphine dosages compared with the usual intake to maximize drug effects.

However, our study has limitations. Inherent in the study design is the problem that, after administration of either diacetylmorphine or saline placebo, the blindedness of both the participants and administering doctor was partially broken, as the pharmacodynamic effects of the administered substance were recognizable. After injection, all were able to correctly guess which agent had been given. Nevertheless, we attempted to maintain the study blind as much as was possible. In addition, the relatively small number of study participants may have lowered the sensitivity of differences in rCBF between drug and placebo, and a concomitant consumption of cannabis, benzodiazepines

### Table 2 Results

| Tableau 2 Résultats
| --- |

<table>
<thead>
<tr>
<th>Regional cerebral blood flow (rCBF)</th>
<th>Values</th>
<th>Two tailed, paired t-test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Right</td>
<td>Left</td>
</tr>
<tr>
<td>Amygdala</td>
<td>0.9 ± 0.4</td>
<td>0.6 ± 0.3</td>
</tr>
<tr>
<td>Vermis</td>
<td>0.8 ± 0.2</td>
<td>0.6 ± 0.1</td>
</tr>
<tr>
<td>Anterior cingulate</td>
<td>0.6 ± 0.1</td>
<td>0.5 ± 0.1</td>
</tr>
<tr>
<td>Thalamus</td>
<td>0.7 ± 0.2</td>
<td>0.5 ± 0.1</td>
</tr>
<tr>
<td>Others</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pupil diameter</td>
<td>Before heroin (mm²)</td>
<td>27.0 ± 5.0</td>
</tr>
<tr>
<td></td>
<td>After heroin (mm²)</td>
<td>23337 ± 7400</td>
</tr>
<tr>
<td>Blood oxygenation</td>
<td>19279 ± 2580000</td>
<td>20014 ± 16720000</td>
</tr>
<tr>
<td></td>
<td>0.7 ± 0.2</td>
<td>0.5 ± 0.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Pattern of regional cerebral blood-flow changes induced by acute heroin administration - a perfusion MRI study

and/or nicotine may have influenced our results. This might also be said of the mild-to-moderate craving noted in almost all participants before receiving their injections. However, given our crossover design, such effects should have been strongly limited.

Our investigation was the first to look at the acute effects of intravenous diacetylmorphine in humans, using fMRI in a setting as close to real life as possible in heroin addicts. We demonstrated that it is possible to detect blood-flow changes using echoplanar MRI techniques. Indeed, this also demonstrates how these techniques can be used for so-called pharmacological imaging, or phMRI techniques, which will undoubtedly have wide applications in patient management and research (both clinical and preclinical). The significance of the increased rCBF in the amygdala after diacetylmorphine administration with clinical). The significance of the increased rCBF in the amygdala after diacetylmorphine administration with respect to the characteristic heroin-induced 'rush', and its relevance to the pathophysiology of opioid addiction, remains to be further investigated.

References