# Buprenorphine Reduces Cerebral Glucose Metabolism in Polydrug Abusers

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*Buprenorphine is a mixed opioid agonist-antagonist, which acts as a partial mu agonist and a kappa antagonist. The present study evaluated the acute effects of buprenorphine on cerebral glucose metabolism (CMRglc) in six human substance abusers using a double-blind, placebo-controlled, counterbalanced, crossover design. Each subject participated in two positron emission tomographic (PET) studies, 1 week apart, following the injection of buprenorphine (1 mg, intramuscularly) and placebo. Buprenorphine significantly reduced CMRglc and the regional cerebral metabolic rate for glucose (rCMRglc) by up to 32% in all but three of 22 bilateral and in 4 midline regions ($p < .05$). No region showed an increase in rCMRglc. Buprenorphine also produced miosis, respiratory depression, and subjective ratings of euphoria and sedation in comparison to placebo ($p < .05$). These observations extend previous findings of reduced CMRglc following acute treatment with morphine and other nonopioid euphorigenic drugs.*
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Buprenorphine, a semi-synthetic opioid drug derived from thebaine, is currently marketed in the United States as an analgesic, and is approximately 25 to 50 times as potent as morphine (Cowan et al. 1977). In human subjects, it produces effects that are typical of opioid agonists (Heel et al. 1979). These include analgesia, euphoria, sedation, pupillary constriction, and respiratory depression. Unlike many opioid agonists, its use is associated with limited physical dependence and minimal withdrawal symptoms (Jasinski et al. 1978; Fudala et al. 1990). Buprenorphine competes with selective ligands for binding to *mu*, *delta*, and *kappa* opioid receptors (Hambrook and Rance 1976; Dum and Herz 1981; Villiger and Taylor 1981; Sadee et al. 1982). Preclinical studies have characterized the in vivo pharmacological activity of buprenorphine as that of a partial *mu* agonist (Martin et al. 1976; Cowan et al. 1977) and a *kappa* antagonist (Leander 1988; Negus and Dykstra 1988). Its unique pharmacological profile has led to the systematic evaluation and development of buprenorphine as a pharmacotherapy for opiate dependence and detoxification (Jasinski et al. 1978; Bickel et al. 1988; Johnson et al. 1992).

Although opioid receptors are widely distributed throughout the human brain, the density and patterns of distribution vary among receptor subtypes. Postmortem studies have revealed high concentrations of *mu*

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receptors in striatum, amygdala, thalamus, and hypothalamus; moderate levels of binding in neocortex (especially frontal and temporal regions); and limited binding in the pons and cerebellar cortex (Kuhar et al. 1973; Pfeiffer et al. 1982). In contrast, *kappa* receptors are most abundant in neocortex (especially layers V and VI), amygdala, and hypothalamus, whereas very low densities are present in most regions of the extrapyramidal motor system and the ventral tegmental area (Pfeiffer et al. 1982; Maurer et al., 1983).

The present study was conducted to evaluate the in vivo effects of buprenorphine in the human brain. One approach to assessment of local brain function is metabolic mapping with 2-deoxyglucose (Sokoloff et al. 1977; McCulloch 1982; Sokoloff 1983). Because glucose is a major substrate for cerebral energy metabolism (Sokoloff 1977; Siesjö 1978), measurement of the regional cerebral metabolic rate for glucose (rCMRglc) provides an index of local brain function (Sokoloff 1977; Sokoloff 1978). The 2-deoxyglucose method, which was developed in rats (Sokoloff et al. 1977), has been extended to human studies, using positron emission tomography (PET) and [F-18]fluorodeoxyglucose [FDG] (Phelps et al. 1979; Reivich et al. 1979) as a radiotracer for glucose metabolism. In a previous study, a euphorigenic dose (30 mg) of morphine, a full agonist acting primarily at *mu* receptors with lower affinity for *delta* and *kappa* receptors (Jaffe and Martin 1990), reduced cerebral glucose utilization in human volunteers with histories of polydrug abuse (London et al. 1990a). The present study similarly examined the acute effects of buprenorphine on global cerebral metabolic rate for glucose (CMRglc) and rCMRglc in human subjects with histories of substance abuse. Simultaneous measures of subjective and physiological responses were obtained. As both morphine and buprenorphine produce positive effects on mood and interact primarily with *mu* opioid receptors, we hypothesized that buprenorphine would decrease CMRglc and rCMRglc, as did morphine. Nonetheless, we reasoned that the differences between the drugs in the spectra of affinities and actions at opioid receptor subtypes would be reflected in the anatomical distribution of rCMRglc changes.

## METHODS

### Subjects

The research subjects were adult male volunteers, recruited through local newspaper advertisements and paid for their participation. The study was completed while subjects resided at the General Clinical Research Center of Francis Scott Key Medical Center. The study was approved by the Institutional Review Boards of Johns Hopkins Medical Institutions and the affiliated Francis Scott Key Medical Center. Subjects gave their written informed consent. An inclusion criterion for the subjects was current, sporadic opiate use without evidence of physical dependence on opiates, as determined by history, observation, and urinalysis.

Aside from substance abuse and associated minor abnormalities in hepatic function, the subjects were deemed healthy according to results of a complete physical examination, electrocardiogram, and blood and urine assays. Urine specimens were collected prior to admission and daily throughout the study. Specimens were tested for the presence of illicit drugs using an EMIT system (Syva Co., Palo Alto, CA) and/or thin-layer chromatography to ensure the absence of drugs other than those administered as part of the research protocol; no illicit drug use was found during the study. The subjects were maintained on a caffeine-free diet, but were allowed free access to cigarettes for 3 days prior to the first PET study and for the intervening week between the two PET studies.

A total of nine subjects enrolled in the study; however, three were excluded prior to completion of the study for the following reasons: two because of a reported head injury prior to admission, and one because of a vasovagal reaction to insertion of an arterial catheter in preparation for the first PET measurement. All subjects were in a drug-free state and were abstinent from all drugs of abuse (except for nicotine) prior to participation in the first PET study.

The six subjects (ages 28 to 36 [mean = 31]) who completed the study were right-handed, black males with histories of intravenous drug abuse. Self-reports of drug-use history were obtained by personal interview (Table 1). All subjects reported drinking alcohol, smoking cigarettes, and using cocaine and heroin intravenously. Two subjects reported using marijuana. The reported use of alcohol ranged from 1 to 2, to 60 drinks per week; cigarettes smoked per day ranged from 4 to 10; marijuana use ranged from 0 to 24 joints per week; cocaine use ranged from 0.15 to 6.0 grams per week; and heroin use ranged from less than 2 to 50 mg per week. None of the subjects reported use of hallucinogens. Some subjects responded positively to questions about drug use, but did not provide meaningful information regarding the amount and/or duration of drug use.

### Experimental Design

The study was a double-blind, placebo-controlled crossover. Each subject completing the study participated in two PET measurements of CMRglc and rCMRglc, 1 week apart, following administration of either 1 mg of buprenorphine or placebo (sterile water) according to a counterbalanced randomized schedule.

**Table 1.** Histories of Drug Use Obtained by Self-Reports[a]

| | | Alcohol | | Nicotine | | Marijuana | | Cocaine | | Heroin | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Subject No. | Age (Years) | Drinks per Week | Duration (Years) | Cigarettes per Day | Duration (Years) | Joints per Week | Duration (Years) | Grams per Week | Duration (Years) | mg per Week | Duration (Years) |
| 1 | 28 | 36 | 18 | 4 | 14 | 24 | 15 | 6 | 10 | 50 | 10 |
| 2 | 29 | + | 8 | 4 | 8 | + | 15 | + | 9 | + | 8 |
| 3 | 29 | 1–2 | 13 | 10 | 10 | 1 | 13 | 0.4 | 9 | <2 | 5 |
| 4 | 30 | 9 | 7 | 10 | 19 | <1 | 16 | 0.8 | 5 | 20 | 5.5 |
| 5 | 33 | 60 | 14 | 10 | 15 | 0 | 0 | 0.15 | 2 | <2 | 2 |
| 6 | 36 | 24 | 12 | 10 | 13 | + | + | 0.15 | 7 | + | + |

[a] Data shown indicate level of current use and duration of use.
+, indicates a positive response without a quantitative report.

### Test Compounds and Radiotracer Preparation

Buprenorphine HCl (Buprenex®) (Reckitt and Colman Pharmaceutical Division, Kingston-upon-Hull, England) was obtained at a concentration of 0.324 mg/ml, equivalent to 0.3 mg/ml buprenorphine base. Buprenorphine (1 mg) and placebo were injected intramuscularly (IM) in a volume of 3.3 ml, divided into two 1.65-ml injections, and administered serially to the right and left deltoid muscles. Buprenorphine and placebo were prepared aseptically under a laminar flow hood by passing the solutions through a 0.22 μm disposable filter (Millipore Products Division, Bedford, MA) into a sterile, pyrogen-free vial (Lyphomed, Inc., Rosemont, IL).

FDG was synthesized from [$^{18}$F]-fluoride produced in a biomedical cyclotron (MC-16F, Scanditronix, Uppsala, Sweden) by the ($p$, $n$) reaction on 98% enriched [$^{18}$O]-labeled water. The radiochemical purity of the final product, determined using thin-layer chromatography or high-performance liquid chromatography on an amino column eluted with aqueous acetonitrile, was greater than 98%. All preparations were sterile and apyrogenic.

### Training and Preparation for PET Studies

Subjects were trained during the first week of admission prior to PET scanning in order to familiarize them with the procedures and to reduce the stress and novelty of the test sessions. During each of two training sessions, the subject was seated in a quiet room with a trained research assistant and instructed to respond to the questions as though he had received either placebo or an opiate drug. The subject's eyes were covered with cotton gauze patches, and he wore headphones that presented constant white noise and a "beep" prompt every minute to both ears. When presented with each prompt, subjects were instructed to respond verbally to the question "How much do you feel the drug?", on a 5-point scale where 0 = not at all, 1 = a little, 2 = moderately, 3 = quite a bit, and 4 = extremely. Responses to beep prompts were obtained at 1 minute intervals for 30 consecutive minutes. Following removal of the blindfold and headphones, subjects provided written responses on each of the questionnaires described below.

Each subject was fitted with a molded thermoplastic face mask that served as a head-stabilization device and alignment guide. Lines were drawn on the mask parallel to the inferior orbitomeatal (IOM) plane and at 48, 56, 64, and 72 mm above this plane. The IOM plane was determined by external landmarks (the inferior orbital notch and the tragus). The lines were used as guides for placement of the subject during the magnetic resonance imaging (MRI), x-ray computer assisted tomographic (CT), and PET scans.

All subjects received structural brain scans by either MRI or CT to verify the absence of abnormal brain morphology. The images from these scans were coregistered with those from the PET scans to enhance accuracy of placement of regions of interest (ROIs) on the PET scans. Four of the subjects received MRI scans using a Resonex 4000 scanner (field strength = 0.4 Tesla, Te = 30 ms, Tr = 1450 ms, 256 × 256 matrix, two interleaved plane sets) producing a proton density-weighted image. One subject was studied using a GE Signa scanner (field strength = 1.5 Tesla) (Te = 20 ms, Tr = 600 ms, matrix 256 × 256, two interleaved plane sets) producing a T1-weighted image. One subject received a CT scan using a Somatom DR 3 CT scanner. The MRI data sets comprised 25 image planes, each 4 mm thick on 4-mm centers, with no gap or overlap. The CT scans comprised 13 planes, each 8 mm thick on 8-mm centers, with no gap or overlap. All image plane sets covered from at least 8 to 104 mm above the IOM plane. Lines drawn on the face mask allowed placement and orientation of the slices to be parallel to and contained within the 12 PET planes that were sampled; they had a nominal thickness of 14 mm on 8-mm centers, and a 6-mm overlap on each side.

### Assay of Plasma Buprenorphine

Buprenorphine levels in arterial plasma (baseline and 45 minutes after test compound injection) were assayed in duplicate with a double antibody radioimmunoassay (Diagnostics Products Corp., Los Angeles, CA). Values are reported as "buprenorphine equivalents" because the antibody cross-reacts approximately equally with buprenorphine and norbuprenorphine at low concentrations (1 to 5 ng/ml). Cross-reactivity with buprenorphine-3-glucuronide is observed at higher concentrations. The sensitivity of the assay was approximately 0.1 ng/ml. The intra- and interassay coefficients of variation averaged 6.6% and 14.0%, respectively.

### Physiological Measures

Pupillary diameter was determined from photographs taken in ambient room lighting using a Polaroid camera with a 3× magnification 30 minutes prior to and at 50 and 100 minutes following injection of the test compound. Heart rate and blood pressure were measured while the subjects were seated at −75, −20, −10, 0, 15, and 45 minutes, and respiratory rate and oral temperature were taken at −75 and 45 minutes with respect to injection of the test compound at time zero. Arterial blood samples were collected for determination of $Pa_{O_2}$, $Pa_{CO_2}$, pH, and bicarbonate at baseline and 13, 28, 45, 60, 90, and 120 minutes after injection of the test compound.

### Subjective Measures

Responses to the beep prompts were obtained at 1-minute intervals for 15 minutes prior to and 30 minutes following injection of the test compound. Other self-reported measures were paper and pencil tasks, and included visual analog scales, a short form of the Addiction Research Center Inventory (ARCI) (Martin et al. 1971), the Single Dose Questionnaire (SDQ) (Jaskinski 1977), and the Profile of Mood States (POMS) (McNair et al. 1971). These questionnaires were administered at 30 minutes before and at 50 and 100 minutes after injection of the test compound. The visual analog scales were presented as 10 cm lines, marked on the left side with the description "not at all," and on the right side with "extremely." Along the analog line, the subject marked his response to the following questions: "How strong was the drug effect?," "How much did you like the drug?," "Did the drug have any good effects?," "How high did you feel?," "Do you want to take this drug again?," and "How much do you desire opiates right now?." The short form of the ARCI consists of forty-nine true/false questions and contains five major sub-scales: Morphine-Benzedrine Group (MBG) [an index of euphoria]; Pentobarbital, Chlorpromazine, Alcohol Group (PCAG) [an index of sedation]; Lysergic Acid Diethylamide (LSD) [an index of somatic sensations and dysphoria]; and the Benzedrine Group and Amphetamine scales [empirically derived amphetamine-sensitive scales] (Martin et al. 1971). On the pharmacological class questionnaire, the subject categorized the drug effect as being most similar to one of ten classes of psychoactive drugs; the questionnaire provided descriptive titles for and examples of each of the following classes: placebo, opiates, opiate antagonists, phenothiazines, barbiturates and sleeping medications, antidepressants, hallucinogens, benzodiazepines, stimulants, and others.

### PET Measurement of rCMRglc

On each day that PET scanning was performed, subjects received a standard nonketogenic 358 calorie (18 g protein, 43 g carbohydrates, and 10 g fat) breakfast. They were then fasted for 4 to 6 hours before the FDG injection, which occurred between 11:00 AM and 2:30 PM. They were not allowed to smoke for 6 hours before the FDG injection and during the radiotracer uptake and scanning. An intravenous infusion of 0.45% NaCl was initiated in a forearm vein at least 3 hours prior to the FDG injection. A radial arterial catheter was also inserted after the administration of local anesthetic (0.5% lidocaine HCl, subcutaneously) in the arm opposite to the venous catheter. Thirty minutes before injection of the test compound, the subject was seated with eyes covered and headphones in place and instructed to relax. At 15 minutes after the injection of test compound, 5 mCi of FDG in NaCl (volume ranged from 2.5 to 6.5 ml) was infused through the forearm vein catheter over 30 seconds, followed by 20 to 50 ml of 0.9% NaCl. The 15-minute interval between injection of FDG and buprenorphine was selected because physiological and subjective responses to buprenorphine have been observed within 15 to 30 minutes of subcutaneous and intramuscular administration of the drug (Jasinski et al. 1989; Ouellete 1982).

Approximately thirty 1.0 to 1.5 ml arterial blood samples were drawn according to a schedule of decreasing frequency, beginning immediately after commencement of the FDG injection and continuing until the end of PET scanning. Blood samples were centrifuged, and aliquots of plasma were assayed for radioactivity and glucose concentration in a well scintillation spectrometer and a glucose analyzer (Glucose Analyzer 2, Beckman Instruments, Irvine, CA), respectively.

As is the common procedure, PET scanning began 45 minutes after FDG injection (Reivich et al. 1979; Phelps et al. 1979). Scanning continued for up to 75 minutes, using the NeuroECAT tomograph (Computers Technology and Imaging, Knoxville, TN) in the

high-resolution mode. The resolution of the scanner is approximately 8 mm within-plane and 14 mm axially. Four 15-minute consecutive scans were performed, each comprising a set of three planes on 32-mm centers. Twelve images, on 8-mm centers and all parallel to the IOM line, were obtained. The lowest plane was 16 mm above the IOM line, and the highest was 104 mm above the IOM line. There were approximately two million true coincidence counts per image.

PET images were reconstructed from the raw data with a standard filtered back-projection algorithm and a high-resolution Shepp-Logan filter with a resolution of 8 mm. Attenuation correction was performed by visually placing an ellipse around the contour of the scalp on the reconstructed PET image. Attenuation was calculated assuming a uniform attenuation coefficient ($\mu = 0.088$/cm, measured for water in the NeuroECAT scanner), and the raw data were corrected and reconstructed again.

Measures of brain radioactivity were converted into estimates of metabolic rates from PET data, plasma radioactivity, and glucose concentration, using published values of the rate constants for the transport of FDG between brain and plasma, FDG phosphorylation and dephosphorylation in brain ($K_1 = .102\ min^{-1}$, $K_2 = .13\ min^{-1}$, $K_3 = .062\ min^{-1}$, and $K_4 = .0068\ min^{-1}$), the lumped constant (LC = .43), and an operation equation (Huang et al. 1980). The PET scanner and the well counter were cross-calibrated daily using a cylindrical phantom containing 1 to 2 mCi of FDG in water.

Data from PET scans were converted to values of rCMRglc and were displayed with an image analysis system (LOATS Associates Inc., Westminster, MD). The resultant images, together with the associated MRI or CT images, were transferred to the IMAGE 1.44 program run on a Macintosh computer (Rasband 1990). A standard template of ROIs was constructed with reference to an anatomical atlas (Hanaway et al. 1980). The template consisted of 42 circles and six ellipses that identified brain areas in eight of the 25 MRI slices. For five of the subjects, MRI and PET scans from each study were compared with the anatomical atlas to select those eight planes that best matched the planes in the reference set for the ROI analysis. It was not possible to obtain MRI scans for one of the subjects; in this case, images from the CT scan were used for co-registration with PET scans.

The size selected for each ROI was based upon the size of the brain area and the spatial resolution of the PET scanner. Ventricles and non-brain matter (bone and cerebrospinal fluid) were excluded from measurement by visual inspection of the densities of structural images. For isolated structures (e.g., caudate nucleus), the ROI was made to fit within the structure; for contiguous areas (e.g., cortical gyri), the ROIs were 7 to 15 mm in diameter. To minimize partial volume effects in small structures, a single ROI was placed on that slice that best passed through the middle of the structure, even if the structure was visible in adjacent slices.

ROI analysis was performed by two independent raters (S. Gilson and J. Schmidt). The drug treatment for each PET study was concealed from both raters. Each of the 48 ROIs was transferred from the standard templates onto the eight MRI or CT slices selected for each subject. Minor adjustments in placement of the ROIs were performed as indicated by anatomical landmarks in the structural image. Structural (MRI or CT) and PET images were then manually co-registered using visual cues, particularly outer edges in the overlaid images. The ROIs were transferred using a modified version of the IMAGE 1.44 program for ROI placement and analysis (Rasband 1990). Inter-rater reliability was tested with Pearson correlation coefficients. The criterion for acceptability of agreement between the raters was arbitrarily set at a correlation coefficient no greater than 0.8 for each individual subject. The criterion of $r = 0.8$ was selected because it is the minimum $r$ that differs significantly from zero at $p = .05$ and $n = 6$. When the coefficient was less than 0.8, the ROIs were placed again and measurements retaken.

Whole-slice and whole-brain average CMRglc were determined by tracing the outlines of the brain on structural images that were co-registered with the PET images and transferring the outlines to the PET images. The brain contour was determined by using visual cues for segmentation of brain tissue from ventricles and extracerebral tissues. The process involved a threshold-based tracing algorithm with subsequent visual correction. The area-weighted average of glucose metabolism in the whole slice was calculated from the metabolic rate in each pixel included within the contour. Global CMRglc was calculated as an area-weighted average of all pixels within the contours of all slices used in the study and was used as the denominator to calculate normalized rCMRglc.

### Statistical Analysis

Data were analyzed using the Statistical Analysis System (SAS) Version 6.07 (SAS Institute, Inc., Cary, NC). All statistical tests were two-tailed, and the criterion for significance was $p < .05$. Data obtained in assays of CMRglc and rCMRglc were subjected to a separate analysis of variance (ANOVA) for each brain region. In cases of midline structures, the ANOVA was one-way, testing the effect of buprenorphine. Data from bilateral regions were analyzed by two-way ANOVA with hemisphere and drug treatment as the factors. Values of $F$ were not corrected for multiple comparisons. When significant $F$ values were obtained for main effects, individual means were compared using Tukey's post hoc tests (with Bonferroni corrections when appropriate).

Repeated measures data were adjusted for sphericity using either the Geiser-Greenhouse or Huynh-Feldt correction equations.

Values for cardiovascular measures (systolic and diastolic blood pressure, heart rate), arterial blood gases ($Pa_{CO_2}$ and $Pa_{O_2}$), pH, and subjective effects were analyzed using two-way ANOVA, with drug treatment (placebo, buprenorphine) and time of measurement as the factors. Post hoc comparisons determined the time when changes from baseline were statistically significant after buprenorphine or placebo administration. Plasma glucose concentrations were averaged over the PET measurement period and were analyzed by Student's paired *t*-test.

## RESULTS

Plasma samples taken before and at 45 minutes after injection of placebo (30 minutes after injection of FDG) were negative for buprenorphine. The mean (SD) buprenorphine level at 45 minutes after injection of the drug was 5.48 (1.67) ng/ml, indicating that buprenorphine was absorbed during the period of FDG uptake.

### Physiological Effects

Data on physiological parameters are shown in Table 2. Buprenorphine significantly constricted pupil diameter in comparison to placebo ($F[1,5] = 39.75$; $p < .001$). The maximum miotic effect was a reduction of pupillary diameter from ~ 4.8 mm before to 2.9 mm at 100 minutes after buprenorphine administration. This effect was observed about 45 minutes after administration of the drug (30 minutes after FDG injection) (Tukey; $p < .05$), indicating that buprenorphine was centrally active during the radiotracer uptake period.

Neither placebo nor buprenorphine had significant effects on heart rate, systolic or diastolic blood pressures, or body temperature. There was a significant drug × time interaction ($F[1,5] = 10.43$; $p = .023$) on respiration, whereby buprenorphine reduced respiratory rate by approximately three breaths/min at 60 minutes after administration of the drug.

Buprenorphine had a very slight but statistically significant hyperglycemic effect. The mean (SD) plasma glucose concentration level for the 30 minute FDG uptake period for the six subjects following injection of buprenorphine was 98.33 (3.19 mg/dl), and 94.04 (3.85 mg/dl) following injection of saline ($p < .05$).

$Pa_{O_2}$, $PA_{CO_2}$, pH, and bicarbonate levels were not significantly altered following placebo administration. In contrast, buprenorphine significantly decreased $Pa_{O_2}$ ($F[1,5] = 77.62$; $p < .001$), and increased $Pa_{CO_2}$ ($F[1,5] = 46.3$; $p < .001$) in arterial blood (Fig. 1). These effects occurred within 30 minutes following buprenorphine administration and were still apparent at the last observation, 2 hours after the injection of buprenor-

**Table 2.** Physiological Responses to Buprenorphine

| Treatment | Sampling Time (min) | Pupil Diameter (mm) | Heart Rate (beats/min) | Systolic Pressure (mm Hg) | Diastolic Pressure (mm Hg) | Temperature (°C) | Respiration (breaths/min) |
|---|---|---|---|---|---|---|---|
| Placebo | −60 | | 64.8 (7.52) | 122 (9.55) | 75.2 (8.01) | 36.8 (0.14) | 14.7 (3.27) |
| | −30 | 5.1 (1.03) | | | | | |
| | −5 | | 64.5 (6.77) | 141 (11.98) | 83.5 (11.22) | | |
| | 5 | | 66.0 (8.67) | 140 (19.40) | 77.2 (10.23) | | |
| | 15 | | 54.7 (20.30) | 139 (19.43) | 78.5 (12.01) | | |
| | 30 | 4.9 (.60) | 63.7 (7.15) | 142 (23.01) | 81.5 (12.74) | | |
| | 60 | | 66.7 (12.36) | 131 (12.66) | 76.5 (7.40) | 36.7 (0.28) | 15.8 (2.56) |
| | 75 | 4.8 (1.10) | | | | | |
| | 120 | | 66.7 (12.36) | 135 (17.91) | 73.3 (9.42) | | |
| Buprenorphine | −60 | | 65.3 (26.63) | 146.5 (9.00) | 80.8 (5.05) | 36.3 (1.33) | 14.8 (1.60) |
| | −30 | 4.8 (1.09) | | | | | |
| | −5 | | 68.2 (13.33) | 144.0 (8.45) | 78.1 (6.05) | | |
| | 5 | | 67.5 (11.58) | 134.8 (7.26) | 76.7 (5.92) | | |
| | 15 | | 66.0 (12.75) | 135.7 (4.84) | 78.3 (5.62) | | |
| | 30 | 3.0 (.48)*† | 62.2 (16.33) | 133.8 (5.27) | 78.8 (4.12) | | |
| | 60 | | 60.7 (21.17) | 130.8 (9.27) | 76.3 (5.01) | 36.5 (0.27) | 12.0 (1.79)# |
| | 75 | 2.9 (.38)*† | | | | | |
| | 120 | | 60.3 (20.46) | 132.2 (8.34) | 77.5 (5.75) | | |

Each value represents the mean (SD) for 6 subjects. Sampling times are relative to the injection of FDG (time = 0), which occurred 15 minutes after the injection of placebo or buprenorphine.

* Significant main effect of buprenorphine by two-way ANOVA and Tukey post hoc tests ($p < .05$).

† Significant main effect of time by two-way ANOVA and Tukey post hoc tests ($p < .05$).

\# Significant treatment by time interaction by two-way ANOVA and Tukey post hoc tests ($p < .05$).

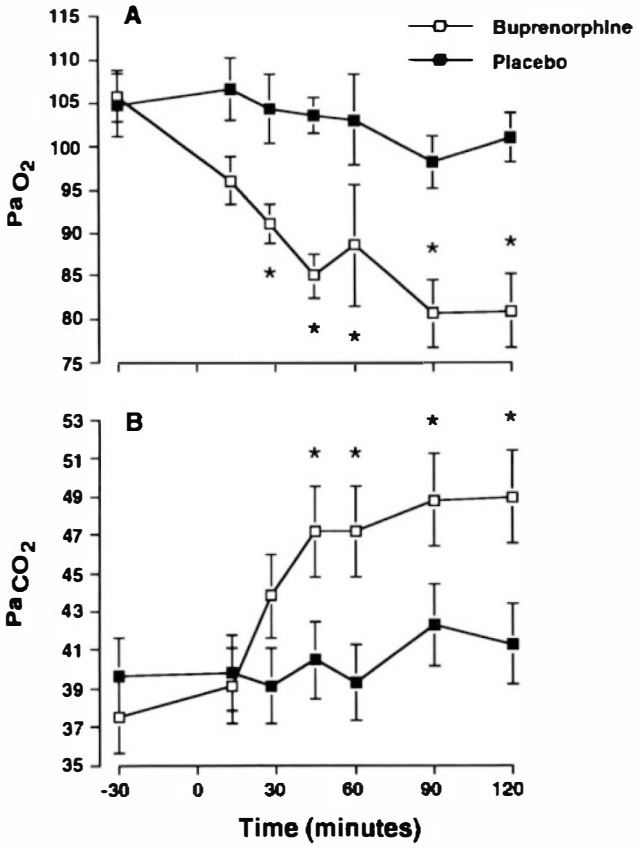


**Figure 1.** Effects of buprenorphine (1 mg, IM, given at time 0) and placebo on arterial blood $Pa_{O_2}$ (A) and $Pa_{CO_2}$ (B). The asterisks (*) indicate significant differences from placebo for each respective time point ($p < .05$; Tukey post hoc analyses).

phine. Arterial blood pH was significantly lowered by buprenorphine ($F[1,5] = 131.1$; $p < .001$); maximal reductions were seen at 120 minutes after drug administration (mean pH [SD] = 7.31 [0.02] vs. pH 7.4 [0.02] at baseline). The bicarbonate level was unaffected (data not shown).

## Subjective Effects

The results obtained on visual analog scales are shown in Figure 2. Measures of positive mood ("good effects" and "high") were significantly elevated by buprenorphine in comparison to placebo ($p < .05$). Subjects reported significant ratings of "drug strength" and "liking" for buprenorphine, and a desire "to take the drug again" ($p < .05$). Buprenorphine produced a small but nonsignificant increase in "desire for opiates." On the SDQ, subjects reported significantly increased ratings of "nodding," "high," "liking," and "feeling the drug" in response to buprenorphine ($p < .05$), but not placebo administration. Buprenorphine had no significant effects on any of the subscales of the POMS.

Analysis of the beep-prompted responses to the question "How much do you feel the drug?" collected during the FDG uptake period revealed significant effects of drug ($F[1,5] = 7.62$; $p = .04$), time ($F[45,225] = 5.56$; $p = 0.27$), and a drug × time interaction ($F[45,225] = 5.14$; $p = .016$). Following administration of placebo, all subjects reported scores of zero, reflecting no subjective drug effect. Following buprenorphine, four of six subjects reported scores greater than zero. For these subjects, recognition of the onset of a drug effect occurred within 7 minutes of the injection on average. Two subjects failed to report a buprenorphine effect in response to the beep-prompt question. However, these two subjects did report significant drug effects on other questionnaires following completion of the FDG uptake period. The average beep prompt scores for the entire group increased from 0 to a maximum of 1.5 following buprenorphine.

Scores on the PCAG scale of the ARCI were higher when the subjects received buprenorphine than when they received placebo ($F[1,5] = 10.0$; $p = .025$). These ratings of sedation increased over time ($F[2,10] = 8.92$; $p = .017$) and were highest at 100 minutes after bupre-

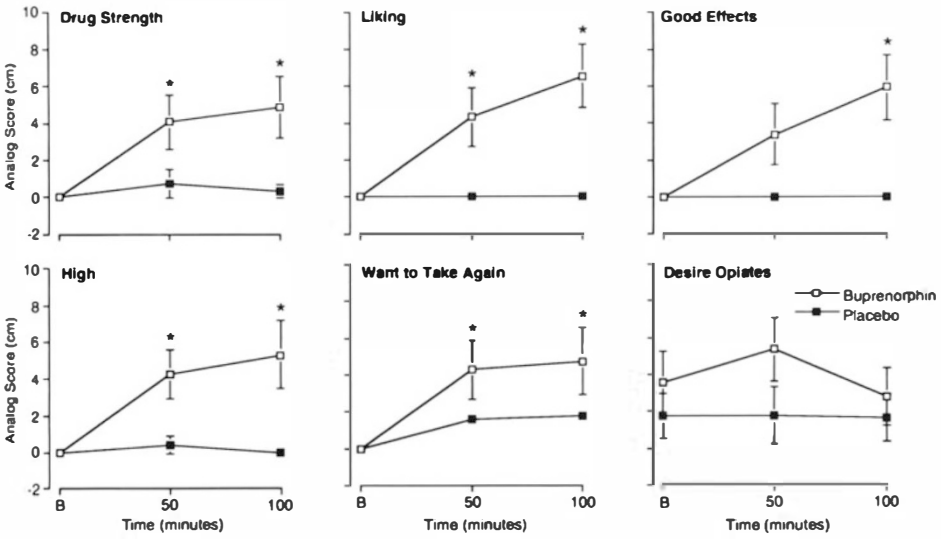


**Figure 2.** The effects of buprenorphine (1 mg, IM, given at time 0) and placebo on six visual analog measures ("drug strength," "liking," "good effects," "high," "want to take the drug again," and "desire for opiates") are shown. The asterisks (*) indicate significant differences from placebo for each respective time point ($p < .05$; Tukey post hoc analyses). B refers to baseline measures collected 15 minutes before injection of drug.

norphine administration. Conversely, scores on the Benzedrine scale were lower after buprenorphine than after placebo ($F[1,5] = 7.03$; $p = .045$). There were no significant main effects on the Amphetamine, MBG, or LSD scales.

### Regional Cerebral Glucose Utilization

Comparison of measurements of rCMRglc in the 48 ROIs (22 bilateral and four midline regions) by two independent raters yielded correlation coefficients ranging from 0.60 to 0.99 for data on individual ROIs. When data were collapsed across ROIs, mean inter-rater correlation coefficients for each of the six subjects ranged from 0.80 to 0.97 (mean = 0.92).

Buprenorphine significantly (both raters) reduced rCMRglc by up to ~ 30% in 17 of the 22 bilateral regions and all midline structures analyzed (Table 3; Fig. 3). The magnitude of the change in rCMRglc was relatively uniform among the regions measured. The superior temporal gyrus demonstrated the smallest reduction in rCMRglc in response to buprenorphine (13.9% and 15.0% in left and right hemispheres, respectively). The largest effects occurred in the medial thalamus (29.5% decrement), the orbitofrontal cortex (26.3% and 30.0% decreases in left and right hemispheres, respectively),

**Table 3.** Effects of Buprenorphine on Regional Cerebral Metabolic Rates for Glucose

| | Regional Cerebral Metabolic Rates for Glucose (mg/100 g/min) | | | |
|---|---|---|---|---|
| | Placebo | | Buprenorphine | |
| **Region** | **Left** | **Right** | **Left** | **Right** |
| Frontal Lobe | | | | |
| Superior frontal gyrus | 6.96 (1.96) | 7.10 (2.09) | 5.69 (0.50) | 5.55 (2.01) |
| Middle frontal gyrus | 8.79 (1.92) | 7.88 (2.77) | 7.02 (0.77) | 6.64 (1.20) |
| Precentral gyrus*† | 7.83 (1.61) | 8.56 (1.41) | 6.10 (0.60) | 6.56 (0.70) |
| Orbitofrontal cortex*† | 5.49 (0.87) | 6.30 (0.96) | 3.97 (0.75) | 4.34 (1.12) |
| Parietal Lobe | | | | |
| Superior parietal lobule* | 7.73 (1.78) | 7.84 (1.90) | 5.38 (0.99) | 5.74 (0.71) |
| Postcentral gyrus* | 7.14 (2.23) | 8.04 (1.66) | 5.32 (1.06) | 5.96 (0.78) |
| Precuneus* | 9.96 (1.62) | 9.79 (1.29) | 7.45 (1.55) | 7.74 (0.82) |
| Temporal Lobe | | | | |
| Temporal pole* | 5.87 (0.61) | 5.96 (0.86) | 4.46 (0.75) | 4.64 (0.57) |
| Superior temporal gyrus* | 5.80 (0.59) | 6.49 (0.66) | 4.98 (0.56) | 5.23 (1.59) |
| Middle temporal gyrus* | 8.14 (0.92) | 8.18 (0.81) | 6.61 (0.74) | 6.80 (1.21) |
| Inferior temporal gyrus* | 7.06 (1.49) | 7.77 (0.91) | 5.49 (1.23) | 5.93 (1.20) |
| Insula*† | 8.41 (1.40) | 8.86 (1.84) | 6.45 (0.89) | 6.93 (0.68) |
| Occipital Lobe | | | | |
| Lateral occipital gyrus* | 6.69 (2.83) | 7.70 (2.16) | 5.33 (2.77) | 6.07 (1.22) |
| Cuneus* | 8.78 (1.70) | 8.18 (1.85) | 5.88 (1.71) | 5.87 (1.137) |
| Limbic Lobe | | | | |
| Cingulate gyrus* | 5.81 (1.45) | 6.72 (1.92) | 4.68 (1.20) | 5.32 (0.90) |
| Amygdala | 5.06 (0.30) | 4.56 (0.36) | 3.63 (0.73) | 3.91 (1.19) |
| Parahippocampal gyrus* | 5.91 (0.82) | 5.72 (0.45) | 4.50 (1.00) | 4.79 (0.59) |
| Hippocampus*# | 5.61 (1.00) | 5.33 (0.49) | 3.90 (0.37) | 4.19 (0.38) |
| Subcortical Regions | | | | |
| Caudate nucleus* | 9.52 (1.52) | 9.02 (1.63) | 7.08 (1.03) | 7.30 (1.48) |
| Putamen* | 9.55 (2.73) | 9.56 (2.74) | 7.12 (1.32) | 6.77 (2.11) |
| Thalamus* | 6.62 (1.30) | 7.04 (2.23) | 5.05 (0.35) | 5.07 (1.32) |
| Cerebellar cortex* | 5.96 (2.31) | 6.61 (1.35) | 4.64 (1.35) | 5.06 (0.92) |
| | **Midline** | | **Midline** | |
| Thalamus* | 7.04 (2.23) | | 5.07 (1.32) | |
| Cerebellar vermis* | 6.01 (0.57) | | 4.56 (0.72) | |
| Pons* | 5.32 (0.87) | | 4.03 (0.55) | |
| Midbrain* | 5.55 (0.42) | | 4.59 (0.64) | |

Each value is the mean (SD) for 6 subjects. Values shown are the average mean of the values obtained by two raters.

* Statistically significant main effect of buprenorphine by two-way ANOVA, $p < .05$.

† Statistically significant main effect of hemisphere by two-way ANOVA, $p < .05$.

\# Statistically significant hemisphere by treatment interaction by two-way ANOVA, $p < .05$.

and the hippocampus (32.7% and 24.4% decreases in the left and right hemispheres, respectively). No statistically significant effect of buprenorphine was demonstrated in the superior frontal gyrus, the middle frontal gyrus, or the amygdala. Moreover, no brain region showed a buprenorphine-induced increase of rCMRglc. There was a significant main effect of hemisphere in the insula, with the right side demonstrating higher rCMRglc than the left, regardless of drug condition. The hippocampus showed a significant hemisphere by drug interaction, with the left hemisphere showing more of a decrease in rCMRglc than the right, although the decrement in both hemispheres was substantial (32.7% and 24.4% in left and right hemispheres, respectively).

Buprenorphine significantly reduced CMRglc by 21.4% [$F(1,5) = 15.2$, $p = .0115$]. Five of the six subjects showed a decrease in response to buprenorphine, whereas one (Subject 5 from Table 1) showed essentially no change (+0.43%). The lack of response by this subject was not accounted for by either a low plasma level of buprenorphine or a self-reported drug history that was markedly different from the rest of the group. Mean (SD) CMRglc values for the six subjects were 6.46 (1.08) and 5.08 (0.72 mg/100g/min) for placebo and buprenorphine treatments, respectively. The decrease in CMRglc ranged from 16.6% to 32.6%, with a median decrease of 21.4%. The correlation between the percent change in CMRglc and buprenorphine levels in plasma failed to reach statistical significance for the small number of subjects tested ($r = .77$).

Normalized values for rCMRglc were obtained by dividing the raw rCMRglc by CMRglc for each subject. Analysis of the normalized data revealed no significant main effects of drug or hemisphere and no significant drug × hemisphere interactions. These findings were consistent across data from the two raters.

## CONCLUSION

The present study is the first demonstration that buprenorphine reduced rCMRglc and CMRglc in human subjects. This effect was global and was consistent with previous findings demonstrating a reduction of CMRglc in response to an equieuphorigenic dose of morphine (London et al. 1990a). Thus, effects on rCMRglc did not distinguish between the actions of morphine, a pure opioid agonist, and buprenorphine, a mixed agonist/antagonist. However, the decrement in CMRglc (21%) following buprenorphine exceeded that observed following morphine (10%). This discrepancy may be attributable to individual differences in the research subjects in the two studies, or to differences in the potencies or receptor binding profiles of the drugs.

Effects of buprenorphine on rCMRglc follow the distribution of opioid receptors in the human brain only to some extent (Kuhar et al. 1973; Frost et al. 1985). For example, some subcortical brain regions (e.g., pons) exhibited decreased metabolism in response to buprenorphine, despite low to negligible levels of opioid receptors. In this regard, the literature on cerebral metabolic responses to psychoactive drugs in rats predicts that the distribution of changes in rCMRglc in response to buprenorphine would not directly parallel the densities of opioid receptors. Discrepancies between rCMRglc changes and the distributions of relevant receptors in brain have been observed using the 2-deoxy-D-[1-$^{14}$C] glucose method in rats treated with a variety of drugs, including muscarinic agonists (Dow-Edwards et al. 1981; Dam et al. 1982), and agonists and antagonists for γ-aminobutyric acid ($GABA_A$) receptors (Palacios et al. 1981). Because values of rCMRglc reflect local, direct interactions with receptors as well as secondary changes that are due to metabolism in afferents (Kennedy 1983), it is plausible that metabolic maps need not reflect relevant receptor maps.

Consistent with the respiratory depressant properties of opioid agonists (Jaffe and Martin 1990) and previous studies with buprenorphine (e.g., Pasqualucci et al. 1987), buprenorphine reduced respiration, as reflected in reductions of respiratory rate and $Pa_{O_2}$ and increases in $Pa_{CO_2}$. It seems unlikely, however, that the decrements in rCMRglc and CMRglc reported here could be due to the mild hypoxia that was produced. First, extreme hypoxia can elevate CMRglc (28% for $Pa_{O_2}$ = 34.6 mm Hg) (Cohen et al. 1967) by stimulating anaerobic glycolysis (Siesjö 1978). Furthermore, although elevated $CO_2$ can reduce cerebral glucose metabolism by inhibiting hexokinase and phosphofructokinase (Siesjö 1978), preliminary studies in our laboratory have shown that hypercapnia at a level similar to that seen in the current study did not reduce CMRglc (J.M. Stapleton, R. Grayson, D.F. Wong, E. Shaya, and E.D. London, unpublished observations). In those studies, four young healthy males were administered 3% to 5% $CO_2$ through a breathing mask prior to and during study with the FDG procedure. When breathing $CO_2$, they manifested mild, statistically nonsignificant hypercapnia [mean $Pa_{CO_2}$ = 41.2 (3.1) and 41.2 (5.25) mm Hg at 15 and 30 minutes after FDG injection vs. 37.8 (4.03) at baseline] and hyperoxia [$Pa_{O_2}$ = 116 (8.06) and 114 (9.90) mm Hg at 15 and 30 minutes after FDG injection vs. 99.5 (7.05) mm Hg at baseline]. When the subjects breathed compressed room air, values of $Pa_{CO_2}$ were 36.7 (3.92) and 38.0 (4.31) mm Hg at 15 and 30 minutes after FDG injection vs. 37.0 (3.48) mm Hg at baseline; values of $Pa_{O_2}$ were 102 (9.32) and 101 (6.10) mm Hg at 15 and 30 minutes after FDG injection vs. 100 (7.28) at baseline. Finally, although the deoxyglucose method measures rCMRglc in the time interval from injection

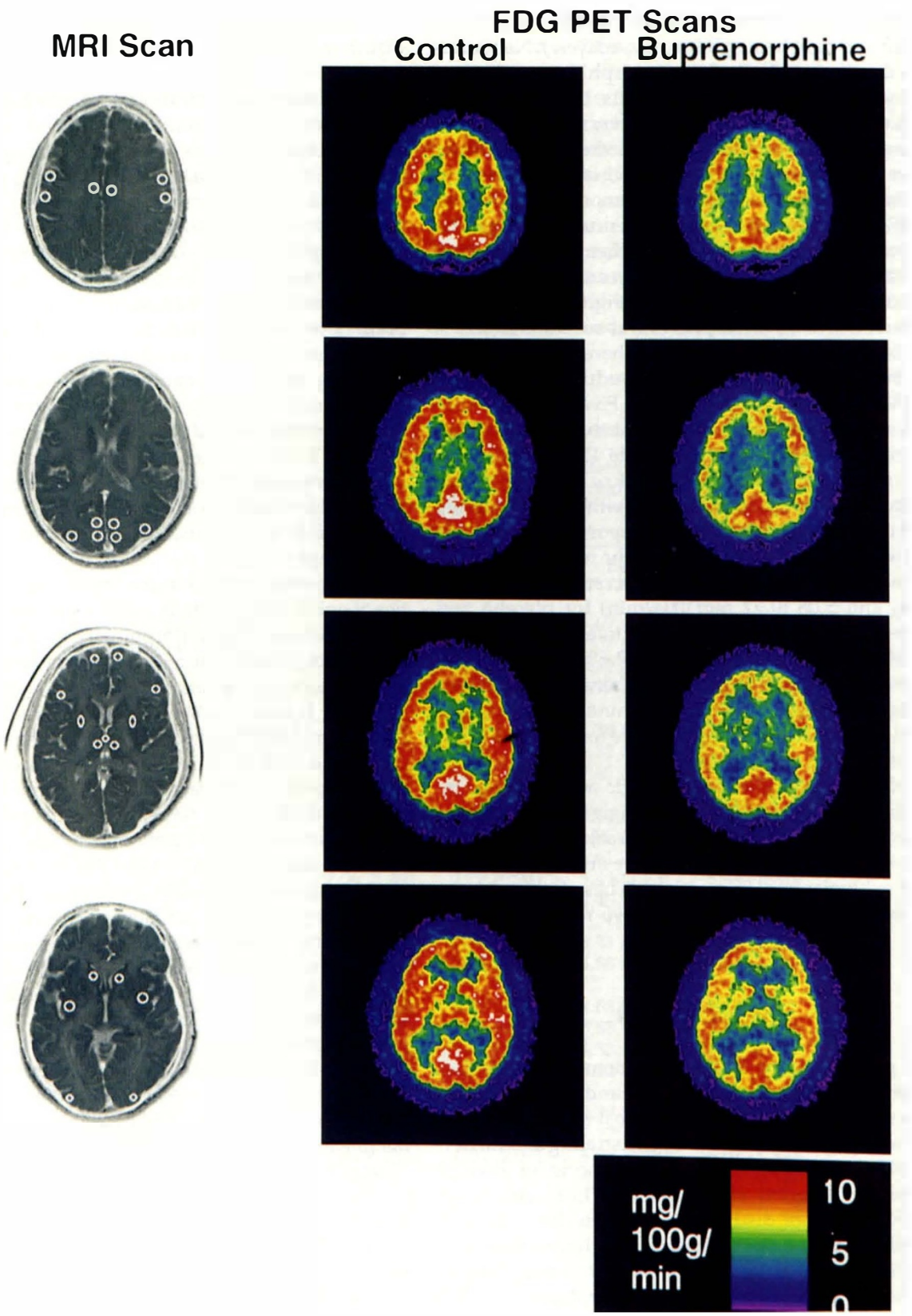


**Figure 3.** MRI scan and color-coded transforms of PET scans showing rCMRglc for a selected subject after treatment with placebo or buprenorphine (1 mg, IM). Placement of ROIs is indicated by white circles and ellipses on the MRI images. Buprenorphine produced statistically significant reductions in rCMRglc by up to 32% (mean for six subjects) in 19 of 22 bilateral and all midline regions.

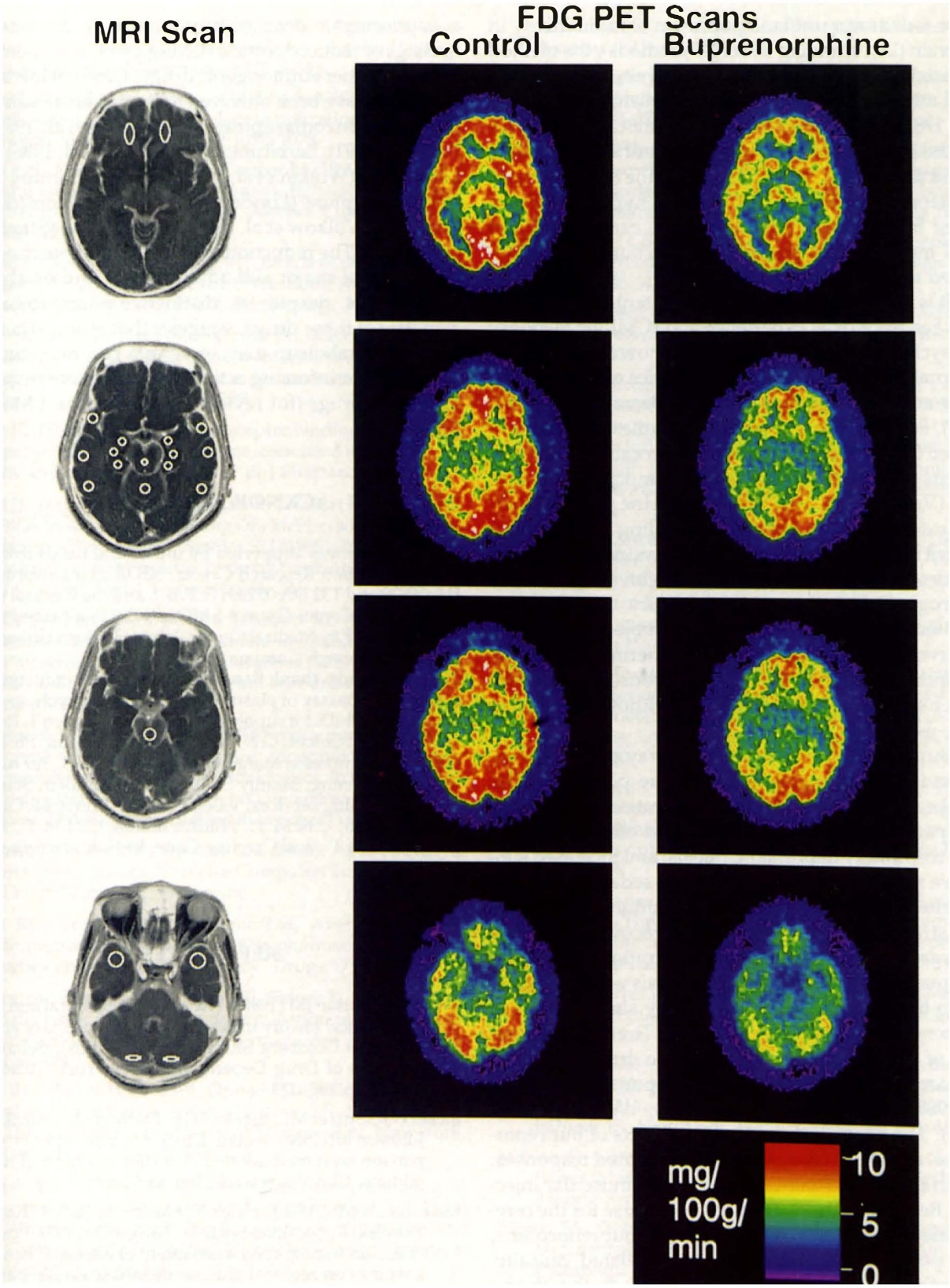


**Figure 3.** *Continued.*

of the radiotracer until measurement of radioactivity in the brain (i.e., scanning with PET methods), the method is biased primarily to reflect brain activity in the first 10 to 15 minutes after radiotracer administration (McCulloch 1982). In the present study, significant hypercapnia and hypoxia were not apparent until approximately 30 and 45 minutes, respectively, after the FDG injection. Therefore, it is unlikely that the mild hypercapnia produced by buprenorphine during the early part of the FDG measurement period could account for the observed decrements in rCMRglc.

It is important to consider the potential interaction between prior drug experience and rCMRglc response to psychoactive drugs. It is well known that the behavioral and pharmacological histories of subjects can influence their response to drugs (Barrett and Witkin 1986). Furthermore, previous PET studies have demonstrated that subjects with histories of cocaine abuse have deficits in glucose metabolism as compared with controls (Volkow et al. 1992). Subjects in the present study had extensive drug histories, including several years of illicit substance abuse, previous physical dependence and detoxification, and experience with a wide variety of drugs. Differences in drug history may have accounted for some of the between-subject differences observed in the present study. Furthermore, pharmacological findings in polysubstance abusers should not be generalized to normal subjects without histories of drug use.

Buprenorphine produced an array of physiological and subjective effects during the period of FDG uptake, consistent with the classification of this drug as a partial *mu* opioid agonist. These effects included mild respiratory depression, miosis, and increased subjective ratings of positive mood and sedation. The miotic effects were evident within 50 minutes of drug administration and showed no sign of recovery at the last measurement, 2 hours after administration of the drug. The magnitude and duration of miosis were comparable to those produced previously by similar doses of buprenorphine (Jasinski et al. 1989). The increased ratings of positive mood, liking for the drug, and sedation are consistent with previous reports (Jaskinski et al. 1989; Preston and Jasinski 1991; Weinhold et al. 1992). The onset of the subjective effects of buprenorphine, as measured by the beep-prompted responses, occurred within 7 minutes of the intramuscular injection. Because of the overlap in time course for the cerebral metabolic and subjective effects of buprenorphine, it is possible that these effects are related causally. Nonetheless, one could only speculate whether the cerebral metabolic response is involved in the neural mechanism that produces the subjective effects or, alternatively, is a response to the subjective effects.

The observed reduction in cortical rCMRglc after a euphorigenic dose of buprenorphine extends the findings of reduced cortical rCMRglc following administration of other euphorigenic drugs. Cerebral metabolic decreases have been observed following acute administration of benzodiazepines (Buchsbaum et al. 1987; de Wit et al. 1991), barbiturates (Theodore et al. 1986), amphetamine (Wolkin et al. 1987), cocaine (London et al. 1990b), morphine (London et al. 1990a), ethanol (de Wit et al. 1990; Volkow et al. 1990), and nicotine (Stapleton et al. 1992). The reduction of cortical metabolism across the range of major self-administered and/or abused drug classes, despite the distinctive pharmacological activities of these drugs, suggests that reduced cortical glucose metabolism may serve as a common component in the reinforcing action and subjective response to abused drugs (for review see London and Morgan 1993).

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