

Cerebral Metabolism in Opiate-Dependent Subjects: Effects of Methadone Maintenance

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Abstract

Background: The long-term effects of opiate use on human brain are not known. The goal of this preliminary study was to determine whether human subjects with histories of opiate dependence have persistent differences in brain function as compared with individuals without substance use disorders, and whether methadone maintenance reverses or ameliorates the potential abnormality.

Methods: Positron emission tomographic (PET) [18F]fluorodeoxyglucose (FDG) method was used to compare the regional cerebral metabolic rate for glucose (rCMRglc) in three groups: four opiate-dependent subjects currently receiving methadone maintenance therapy (MM), four opiate-dependent subjects not receiving methadone maintenance therapy (MW), and a comparison group of five subjects without substance use disorders.

Results: A significant difference in rCMRglc in the anterior cingulate gyrus was found between the MW and Control groups (Mann-Whitney U = 2.0, p = 0.05). Generally speaking, rCMRglc's in MM subjects were intermediate between those of MW and Control groups, although the difference did not reach statistical significance.

Conclusions: The results of this study suggest that neurobiological abnormalities can persist in the brain of a chronic opiate user several years after detoxification from methadone. Future research is needed to replicate these results and to determine whether the observed rCMRglc differences are related to opiate use or to neurochemical abnormalities that play a role in developing addictive behavior.

Key Words: Cerebral metabolism, opiate dependency, methadone maintenance.

Introduction

OPIATE ADDICTION has been a public health problem in the United States for more than 100 years. Since the availability of heroin has increased dramatically in the 1990s, the problem of opiate dependence has become more acute. It has been estimated that more than 2.7 million Americans have used heroin at some time in their lives, and that approximately one million meet the criteria for heroin dependence (1).

Methadone maintenance therapy (MMT) is the primary treatment offered to opiate-dependent patients in this country, and long-term treatment has been evaluated to be crucial for positive outcome (2, 3). Although marked by considerable controversy (patients remain physically dependent on medication, and many continue to use heroin and other illicit drugs), most treatment evaluation studies have shown that methadone maintenance therapy is effective. By binding to opiate receptors in the brain, methadone reduces drug-seeking behaviors, reduces or eliminates use of heroin, prevents opiate withdrawal symptoms, and stabilizes neuroendocrine functions (1, 4, 5). Methadone's long duration of action provides successful treatment with daily dosing, allowing patients to maintain relatively normal patterns of activity.

Methadone maintenance therapy reduces illicit opiate use, decreases the risk of HIV transmission, results in improved general health, and is associated with higher employment rates (3). It also reduces the antisocial behavior that accompanies the use of illicit drugs and the societal costs of opiate dependence (2, 3, 6–9). However, not

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Glossary: FDG [18F]fluorodeoxyglucose, a PET tracer; MM Receiving methadone maintenance; MW Not receiving methadone maintenance; PET Positron Emission Tomography; rCBF Regional cerebral blood flow; rCMRglc Regional cerebral metabolic rate for glucose; ROI Region of interest; SPECT Single Photon Emission Computed Tomography.

all patients respond to the same extent. Polysubstance users, patients with comorbid psychiatric histories, and patients receiving inadequate methadone doses have poorer prognoses than others (2, 3, 6, 10). Nonetheless, the net effect over time typically is the extinction of heroin use (11). Compared to newer medications such as buprenorphine, methadone maintenance therapy is of equal or greater effectiveness, as measured by retention in treatment, decrease in illicit opiate use, rate of abstinence and compliance with counseling (12–14)

The primary goal of this preliminary study was to determine whether human subjects with histories of opiate dependence have persistent differences in brain function as compared with individuals without substance use disorders, and whether methadone maintenance therapy reverses or ameliorates the potential abnormality. To this end, the positron emission tomographic (PET) [18F]fluorodeoxyglucose (FDG) method was used to compare the regional cerebral metabolic rate for glucose (rCMRglc) in three groups: opiate-dependent subjects currently receiving methadone maintenance therapy, opiate-dependent subjects not receiving methadone maintenance therapy, and a comparison group of subjects without substance use disorders.

There have been few brain imaging studies investigating the effects of opiates or opiate antagonist drugs on regional brain function (assessed by measuring regional cerebral blood flow or rCMRglc) in human subjects (15–18). In contrast, the effects of opiate administration on regional cerebral blood flow in subjects without histories of substance use were researched more thoroughly (19–26). These studies implicated the anterior cingulate gyrus as one of the key brain regions subserving pain and opiate-induced analgesia. The leading theories of opiate dependence invoke either the “Endogenous Opioid Deficiency Syndrome” (5) or an “Atypical Stress Responsivity” (27) to explain the disorder. They both posit the existence of excessive emotional pain in opiate users. It was, therefore, of interest to determine if the anterior cingulate gyrus would be among the brain regions to show a methadone-reversible abnormality in opiate-dependent subjects.

Methods

Subjects: Eight subjects diagnosed with opiate-dependence according to DSM-IV (four stabilized with methadone maintenance therapy [MM], four withdrawn from methadone [MW] and five

control subjects participated in this preliminary study). All participants were right-handed. Subjects on MMT were recruited from the 23 methadone clinics operated by Beth Israel Medical Center and the 9 methadone clinics associated with Albert Einstein College of Medicine Hospitals and The Mount Sinai Hospital. For the MW group, subjects in full, sustained remission were recruited from former patients who had remained in contact with their methadone clinic counselors. Control subjects were recruited from support staff at Beth Israel Medical Center. They were somewhat younger than opiate-dependent subjects. The demographic characteristics of the subjects are presented in Table 1.

In order to establish psychiatric diagnoses, the Structured Clinical Interview for DSM-III-R (28) was administered along with the Mini-Mental Status Examination. Urine for toxicology was obtained three times: twice on the days of psychometric testing and once before the PET scan. HIV tests, CBC, and SMA-7 were also obtained from the subjects prior to the PET scan. The subjects were paid for participation in the study.

Subjects were both male and female; they were included in the study if they were between 21 and 45 years of age, and were able to demonstrate an understanding of the study before giving written consent. A DSM-IV diagnosis of opiate dependence in the past 2 years, established by structured clinical interview for diagnosis (SCID), was an inclusion criterion (28). The MM subjects were required to be on a stable dose of methadone for at least 6 months prior to entering the study. A requirement for the MW was a period of at least 6 months since detoxification from methadone maintenance therapy. Subjects were

TABLE 1
Characteristics of Subjects

	Controls	Opiate-dependent Subjects	
		MM	MW
N	5	4	4
Gender (male/female)	3/2	2/2	2/2
Age (yrs)	25.6 ± 1.7	38.0 ± 5.8	38.0 ± 1.4
Education (yrs)	15.0 ± 2.0	11.5 ± 4.7	14.0 ± 3.2
Years of opiate abuse	—	13.6 ± 10.1	7.8 ± 1.7
Years of MMTP	—	4.3 ± 3.4	9 ± 9.4
Years on stable dose of methadone	—	1.5 ± 1.4	—
Years since detoxification	—	—	4.3 ± 1.7

MM = methadone maintenance therapy group
MW = group not receiving maintenance

excluded if they had: a current or lifetime history of any Axis I diagnosis other than opiate dependence and nicotine dependence; a history of cocaine use within the 6 months prior to the study; central nervous system (CNS) disease; cardiovascular, pulmonary or systemic disease; or HIV-seropositivity. Moderate alcohol or caffeine use was not an exclusion criterion.

PET Scanning

Scanning procedure. Brain imaging was performed using a Posicam 6.5 PET scanner (Positron Corp., Houston, TX), and FDG was purchased from the CTI Services, Inc. PET Distribution Center (New York, NY). The Posicam 6.5 is a 21-slice instrument with a 5.125-mm inter-slice distance. The spatial resolution of the tomograph is 5.8 mm in-plane and 11.9 mm in the z-axis. The sensitivity of the camera, measured with a 20-cm diameter cylindrical phantom (system sensitivity), is (165 counts/ $\mu\text{Ci}/\text{cm}^3/\text{axial cm}$).

Prior to injection of the radiotracer, the subject was positioned in the scanner gantry and his/her head was immobilized with a thermoplastic mask. A 20-min transmission scan, using a Ga/Ge rod, was performed to measure the attenuation of photons by the brain and skull. For the FDG injection, a catheter was placed into a left forearm vein. The subjects received one injection of FDG (5 mCi, 185 mSv), and an emission scan (approximately 20 min) was initiated approximately 30 min after the FDG injection. Following the scan, the subject was removed from the tomograph and instructed to void, to reduce the radiation dose to the bladder (29). From the time of the FDG injection until the end of the scan, lighting in the room was dimmed, and the subject was instructed to stay awake but keep his/her eyes closed.

Image Reconstruction. Images were corrected for attenuation and reconstructed utilizing a spatially-varying convolution-scatter subtraction technique and a Butterworth filter. Raw counts were used for PET scan analysis, and the data were transferred to a SUN workstation for image analysis. The global raw counts were measured on all images that contained the brain. The threshold-based region growing algorithm in ANALYZE (Digital Equipment Corp., Houston, TX) was used to outline the brain on all slices in which it appeared. The global raw count was taken as the mean of the mean raw counts for each slice. The raw count image was normalized by dividing the raw count of the specific region of interest by the global raw count of the subject.

Image Analysis. Image analysis was performed by an investigator blind to the identity and diagnosis of each subject. Using a standard template, 38 bilateral regions of interest (ROIs) were placed on PET images and individually adjusted to account for differences in neuroanatomy. The ROIs were: template 1 (left and right temporal pole, left and right cerebellar hemisphere); template 2 (left and right medial orbitofrontal cortices, left and right lateral orbitofrontal cortices, left and right superior temporal cortices, left and right middle temporal cortices, and left and right hippocampi); template 3 (left and right caudate heads, left and right putamens, and left and right thalami); template 4 (left and right ventral superior frontal cortices, left and right ventral middle frontal cortices, and left and right middle occipital cortices); template 5 (left and right anterior cingulate gyri, left and right dorsal superior frontal cortices, left and right lateral dorsal frontal cortices, and left and right angular gyri); and template 6 (left lateral parietal cortex, and left and right dorsal parietal cortices).

Statistical Analysis. In a preliminary screening procedure, potential group differences in rCMRglc were evaluated by separate Kruskal-Wallis ANOVA's, performed on values from each ROI. In order to avoid false positive findings, only the relative magnitudes of the Mann-Whitney U test statistics were examined, and the ROI yielding the lowest value was selected for modeling via Generalized Estimating Equations (30, 31). In the primary analysis, rCMRglc values taken from right- and left-hemispheres in each subject were treated as repeated measures. The model treats rCMRglc as a continuous variable with an approximately Gaussian distribution.

Results

Even unprotected by correction for multiple comparisons, the preliminary data screening procedure yielded only one Mann-Whitney U statistic significant at $p < 0.05$. The significant difference was between the MW and control groups in the anterior cingulate gyrus (Mann-Whitney $U = 2.0$, $p = 0.05$) (Fig. 1). Group descriptive statistics for left and right hemisphere rCMRglc values for the anterior cingulate gyrus are given in Table 2. Accordingly, rCMRglc in anterior cingulate gyrus was regressed on hemisphere (L, R) and group membership (MM, MW, dummy coded with controls as reference) in a Generalized Estimating Equations model:

$$\text{rCMRglc} = \text{Intercept} + \beta_1(\text{Hemisphere}) + \beta_2(\text{Group 1}) + \beta_3(\text{Group 2}).$$

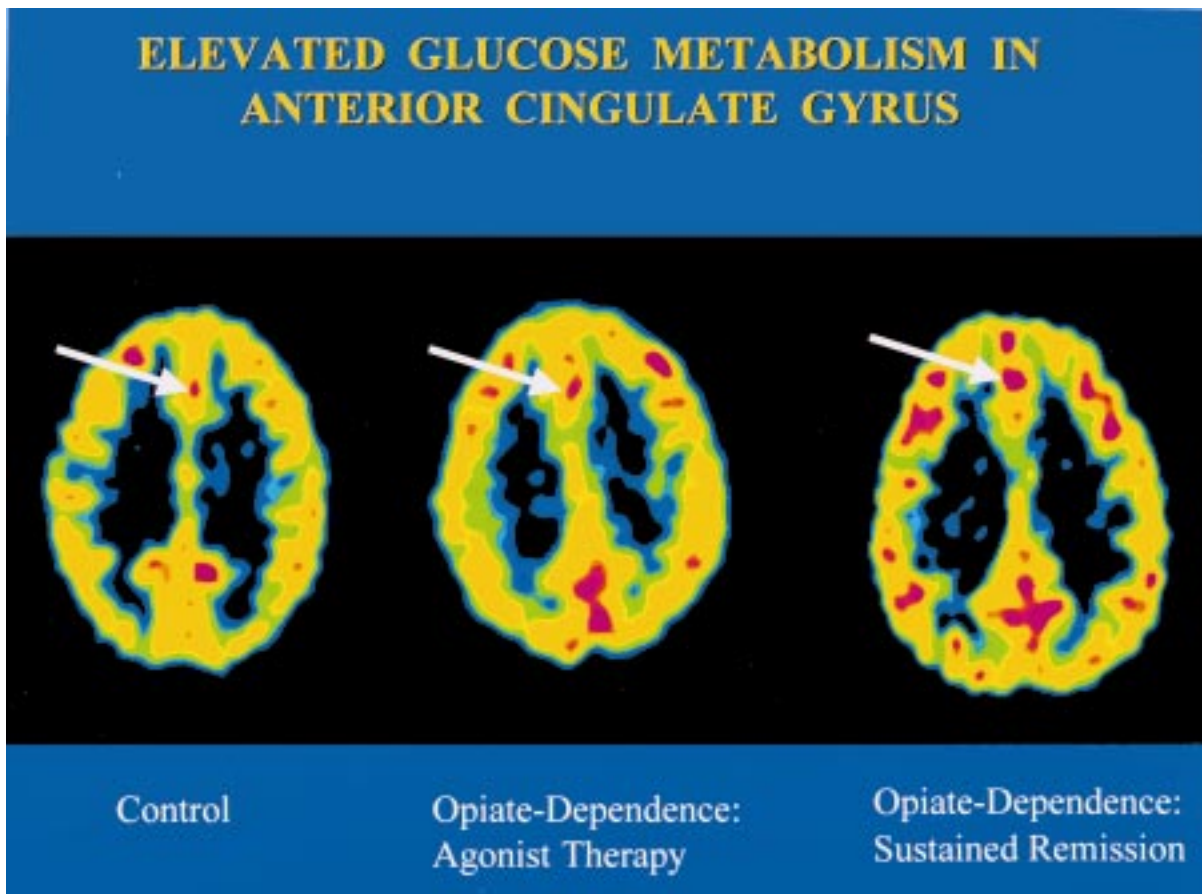


Figure. Brain metabolic images at the level of corpus callosum for methadone-maintained and methadone-withdrawn subjects with histories of opiate dependence and control subjects. Arrows point to the anterior cingulate gyrus where ROIs were placed and activity measured.

TABLE 2
Regional Cerebral Metabolic Rate for Glucose of the Anterior Cingulate Gyrus

	Intercept	Hemisphere	Group 1	Group 2
β	1.3614	0.0303	0.1147	0.1025
S.E.	0.0377	0.0413	0.0299	0.0350

Group 1 = methadone maintenance group
Group 2 = methadone withdrawal group

Overall, the analysis resulted in a Wald χ^2 value = 15.41, (df = 3), $p < 0.01$, with parameter estimates and their standard errors as follows: Here, the β coefficients were effect sizes, scaled to the metric of the dependent measure. Hence, holding hemisphere constant, MM subjects had values of rCMRglc that were 0.1147 $\mu\text{Ci}/\text{mL}$ greater than those of controls and rCMRglc's in MW subjects was 0.1025 $\mu\text{Ci}/\text{mL}$ greater. The model also yielded standardized parameters (Estimate/S.E.) that served as significance tests of the β_i 's. The

test for hemisphere was not significant ($z_H = 0.74$), but those contrasting the MM and MW groups with controls were significant ($z_{MM} = 3.84$, $p < 0.001$ and $z_{MW} = 2.93$, $p < 0.01$). Holding the control group membership constant, further exploration of the contrast between the MM and MW groups was afforded by a Wald test statistic for $H_0: \beta_1 = \beta_2$, which yielded no significant difference ($z = 0.42$). Generally speaking, however, rCMRglc's in MM subjects were intermediate between those of MW and control groups.

These results indicated significantly higher rCMRglc's in both MM and MW subjects compared to that of control subjects. However, in view of the age difference between opiate-dependent subjects and controls, age might have been a confounding factor in this result. In order to address this concern, a *post hoc* analysis was conducted in which each subject's age was added as a covariate to the model tested above; its associated β coefficient is -0.0020 ($z = 0.70$, $p = ns$) and it appeared not to figure importantly in this model.

Discussion

The results of this study suggest that neurobiological abnormalities can persist in the brain of a chronic opiate user several years after detoxification from methadone. At present, there are no data in the literature for direct comparison with the results of this study and there are only a handful of PET and single photon emission computed tomography (SPECT) studies on the effects of acute opiate administration, opiate withdrawal, and chronic opiate use on rCMRglc and regional cerebral blood flow (rCBF). Some of the studies showed changes in the anterior cingulate gyrus; most were performed on polysubstance users.

London et al. (15) used FDG PET methodology to demonstrate that in polydrug abusers, morphine, primarily a mu-opioid agonist, reduced rCMRglc in a number of telencephalic and subcortical structures, with a significant global effect. As buprenorphine, a mixed opioid agonist/antagonist, had similar effects (16), it was suggested that the primary effect on rCMRglc was through an action as a mu-opioid agonist.

Only two preliminary ^{99m}Tc HMPAO (Ceretic, Amesham, Ltd., U.K.) SPECT studies of rCBF during "opiate withdrawal" have been published (17, 18). Krystal et al. (18) reported that in subjects receiving methadone maintenance treatment, symptoms of withdrawal after acute naloxone administration were associated with lower global perfusion, lower activity ratios in the frontal and parietal cortices, and increased thalamic activity. Van Dyck et al. (17) studied the effects of naltrexone-precipitated opiate withdrawal in active heroin users after a 7-day buprenorphine treatment. Compared to placebo, naltrexone-precipitated withdrawal resulted in no significant changes in rCBF ratios, but the severity of opiate withdrawal was negatively correlated with rCBF in the anterior cingulate gyrus. The authors related their finding to a role of anterior cingulate gyrus in processing the emotional, suffering component of pain (21, 32).

The PET and SPECT studies of "chronic opiate" use did not show rCBF and rCMRglc changes in the anterior cingulate gyrus. Krystal et al. (18) studied the effects of chronic opiate use on rCBF using ^{99m}Tc HMPAO SPECT in a group of polysubstance users on methadone maintenance treatment. The extent of illicit drug use in this group is unclear, although with one exception, all subjects were free of drugs, as judged by weekly urine toxicologies and clinical records. The authors reported that subjects on methadone maintenance treatment had lower perfusion rates in the frontal and parietal cortices and greater perfusion rates in the thalamus, compared to healthy controls. In a study of cocaine-using polysubstance users, Holman et al. (33) found a higher number of focal perfusion defects in the temporal, inferior parietal, and anterior frontal cortices of those patients, compared to healthy subjects. A more extended pattern of metabolic abnormalities in polydrug cocaine/opiate abusers involving decreased absolute rCMRglc in the lateral occipital gyrus, temporal, and orbitofrontal cortices was detected in FDG PET studies by Stapleton et al. (34).

In addition to brain studies investigating neurobiological effects of opiates in opiate-dependent subjects, the anterior cingulate gyrus was implicated in PET studies as being one of the key brain regions subserving "analgesia and pain" in subjects without histories of opiate use. Morphine "analgesia" decreased the affective-motivational, but not the sensory dimension of pain in a case report of a patient suffering from cancer (32). In this preliminary study, rCBF measured with PET using C^{15}O_2 revealed that morphine analgesia was associated with an increased perfusion in the temporal, prefrontal and the anterior cingulate gyri (32). Another PET study, this one measuring rCBF in opiate-naive, healthy volunteers showed that fentanyl analgesia increased rCBF in the anterior cingulate gyrus, and motor and prefrontal cortices, and decreased rCBF in the thalamus and posterior cingulate cortex (20). This activation pattern was also associated with decreased pain perception. Both studies demonstrated a similar pattern of activation, including the anterior cingulate gyrus and related prefrontal cortex during opiate administration and analgesia.

A number of rCBF PET studies using ^{15}O -labeled tracers indicate that in healthy subjects, "pain" increases regional cerebral blood flow in the anterior cingulate gyrus, especially Brodmann area 24 (20–26). Pain also resulted in increased activity in the lentiform nucleus, periaqueductal gray, and prefrontal cortex (22, 24,

35); thalamus and supplementary motor area (20, 24); and insula and somatosensory cortex (21, 22, 24). These structures are either a part of or are closely related to the "medial pain system" (36). The anterior cingulate gyrus represents the brain region most consistently activated by pain stimuli.

In view of the above, there are two possible interpretations for our findings: (1) Chronic use of illicit opiates or MM is associated with elevations in the rCMRglc in the anterior cingulate gyrus, which persist after cessation of opiate use, and are long lasting (over several years). From our study design it is impossible to determine whether the observed rCMRglc differences are related to illicit opiate use or result from opiate maintenance. (2) The observed rCMRglc elevations in the MM and MW subjects (compared to controls) preceded opiate use and could be related to neurochemical abnormality that plays a role in developing addictive behavior.

The neurobiological basis for the observed rCMRglc differences in the anterior cingulate gyrus is unclear at this time. Based on early neurosurgical studies as well as on functional brain imaging work detailed above, Vogt et al. (26) proposed that activation of the anterior cingulate gyrus during the pain PET paradigms was associated with the affective-motivational, suffering component of pain. Similar increase in rCBF of the anterior cingulate gyrus was observed during morphine-induced analgesia and associated euphoria (37), suggesting powerful regulation of the anterior cingulate gyrus by opiate compounds (26) and a close relationship between opiates and affect and mood. The relationship between opiate-related elevations in the rCBF in the ventral anterior cingulate gyrus and affect are further supported by reports of similar rCBF elevations during PET studies of sadness in healthy women (38). Therefore, the observed differences in the anterior cingulate gyrus in patients with histories of opiate dependence compared to control subjects are not inconsistent with the existence of excessive emotional pain in opiate abusers posited by "Endogenous Opioid Deficiency" (5) and "Atypical Stress Responsivity" (27) theories of opiate dependence.

The results of this study should be considered within its limitations, which include small sample size, poor demographic matching of the control group to patient groups, and limited spatial resolution of the Posicam PET. Nonetheless, the results of this study suggest that specific neurobiological abnormalities, i.e., elevated rCMRglc in the anterior cingulate gyrus, may persist in brains of chronic opiate users several years after methadone

detoxification. Further research is needed in order to validate these preliminary findings and to explore whether the rCMRglc differences in the anterior cingulate gyrus observed in this study result from or precede opiate dependence.

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