Available online at www.sciencedirect.com

SCIENCE DIRECT®

Psychiatry Research: Neuroimaging 131 (2004) 217–226

PSYCHIATRY RESEARCH NEUROIMAGING

www.elsevier.com/locate/psychresns

Cerebral phosphorus metabolite and transverse relaxation time abnormalities in heroin-dependent subjects at onset of methadone maintenance treatment

Marisa M. Silveri[a,b], Mark H. Pollack[c], Claudia I. Diaz, Leanne E. Nassar[a], Jack H. Mendelson[b], Deborah A. Yurgelun-Todd[a], Perry F. Renshaw[a], Marc J. Kaufman[a,b,*]

[a] *Brain Imaging Center, McLean Hospital, Department of Psychiatry, Harvard Medical School, 115 Mill Street, Belmont, MA 02478, USA*
[b] *Alcohol and Drug Abuse Research Center, McLean Hospital, Department of Psychiatry, Harvard Medical School, Belmont, MA 02478, USA*
[c] *Massachusetts General Hospital and Habit Management Institute, Boston, MA, USA*

Received 8 October 2003; received in revised form 20 May 2004; accepted 21 May 2004

Abstract

Cerebral bioenergetic and phospholipid abnormalities have been reported in heroin-dependent subjects. The goal of the present study was to characterize the neurochemical profile of subjects voluntarily enrolled in a methadone maintenance (MM) treatment program to overcome their heroin addiction. Participants included 43 heroin-dependent subjects during their first month of MM and 15 age-matched healthy individuals. Phosphorus magnetic resonance spectroscopy (^{31}P MRS) and transverse relaxation times (T2-RT), which can reflect steady state cerebral perfusion and metabolism, were acquired at 1.5 T from an axial slice prescribed through the orbitofrontal and occipital cortices, including basal ganglia and frontal cortex. MM subjects exhibited reduced phosphocreatine (PCr) levels (− 15.3%), elevated phosphodiesters (+ 12.9%, PDE) and significantly longer T2-RT ((+) 2.1%) compared with healthy comparison subjects. When MM subjects were stratified into subgroups based on treatment duration, we found a treatment duration effect on metabolite values but not T2-RT; reduced PCr was observed only after 8+ days of MM, and phosphomonoesters (PME) were elevated in the 15–28 day MM group. Taken together, these cross-sectional data suggest that the first month of MM treatment may be associated with altered cerebral bioenergetics and phospholipid metabolite levels.

Keywords: ^{31}P MRS; T2-RT; Heroin; Methadone maintenance; PCr; Phospholipids

1. Introduction

There has been a recent rise in heroin abuse, with 81,000 new heroin users in 1997, in addition to 2.4 million existing heroin users (NIDA, 2000). Moreover, 14% of all drug-related episodes in hospital emergency rooms involve heroin, a figure that dou-

* Corresponding author. Brain Imaging Center, McLean Hospital, Department of Psychiatry, Harvard Medical School, 115 Mill Street, Belmont, MA 02478, USA. Tel.: +1-617-855-3469; fax: +1-617-855-2770.
E-mail address: kaufman@mclean.harvard.edu (M.J. Kaufman).

0925-4927/$ - see front matter © 2004 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.pscychresns.2004.05.003

bled between 1991 and 1996 (SAMHSA, 2001). This increase underscores the importance of studying heroin-associated brain changes.

While imaging studies have revealed a number of cerebral perfusion, metabolic, and metabolite abnormalities in opiate-dependent subjects that may contribute to functional deficits in this population (e.g., Christensen et al., 1996; Danos et al., 1998; Krystal et al., 1995; Levin et al., 1994; London et al., 1989; Rose et al., 1996; Stapleton et al., 1995), at present, few studies have examined the effects of treatment for overcoming opiate dependence on cerebral function. A single photon emission computed tomography (SPECT) study demonstrated reduced cerebral perfusion abnormalities in cocaine- and heroin-dependent men after receiving buprenorphine treatment, although improvement was no longer evident when men tapered off the drug (Levin et al., 1995). Galynker et al. (2000), using positron emission tomography (PET), reported a trend for improved anterior cingulate cerebral metabolism in methadone maintenance (MM) subjects (stabilized in treatment for 1.5 years) relative to subjects withdrawn from MM treatment.

Our group, using phosphorus magnetic resonance spectroscopy (^{31}P MRS) and SPECT, detected abnormal cerebral metabolism and perfusion in cocaine- and opiate-dependent subjects during early MM treatment (Christensen et al., 1996). In a separate cohort of opiate-dependent subjects, examined after extended periods of MM, we also identified cerebral metabolic and phospholipid abnormalities, the magnitude of which diminished with longer treatment duration (Christensen et al., 1996; Kaufman et al., 1999).

The purpose of the present cross-sectional study was to characterize metabolic and phospholipid abnormalities in opiate-dependent subjects shortly after their voluntary enrollment in MM to overcome heroin addiction. Methadone maintenance currently is the treatment of choice for opiate dependence in the United States (Joseph et al., 2000), due in part to its ability to relieve narcotic craving and suppress the opioid abstinence syndrome, and its association with reduced illicit drug use, reduced spread of hepatitis and HIV, and increased employment (Galynker et al., 2000; Kreek and Reisinger, 1997). Because attrition rates are extremely high early in treatment, assessing brain function changes during this period may help to determine why so many patients drop out (Condelli and Dunteman, 1993; Goldstein et al., 2001; Joe et al., 1999; Simpson et al., 1997). In addition to examination of differences between heroin-dependent and healthy comparison subjects, heroin-dependent subjects also were stratified into subgroups based on their duration of MM treatment at the time of the study: 0–7, 8–14, or 15–28 days. Thus, each subject was examined only once during their first month of MM. Since polydrug use often accompanies heroin dependence, additional drug use was monitored using the Addiction Severity Index (McLellan et al., 1985) and a urine toxicology screen prior to imaging.

^{31}P MRS allows measurement of molecules associated with brain bioenergetic status and phospholipid membrane integrity. Bioenergetic status is reflected by levels of adenosine triphosphate (ATP, detected in the beta nucleoside triphosphate (β-NTP) resonance) and in inorganic phosphate (Pi) and phosphocreatine (PCr) resonances. ^{31}P spectra also are composed of markers for membrane integrity and turnover, which include phosphomonoesters (PME; membrane precursors) and phosphodiesters (PDE; lipid catabolites). Based on findings from our prior studies, we predicted that, relative to healthy comparison subjects, MM subjects would exhibit attenuated PCr and β-NTP levels, as well as elevated PME and PDE levels. Since our prior work in opiate-dependent subjects suggested that metabolite abnormalities/profiles might differ as a consequence of treatment duration (Kaufman et al., 1999), we also predicted that stratifying MM subjects into subgroups based on treatment duration would reveal additional information regarding cerebral function during the initiation of MM. Our second aim was to determine whether magnetic resonance T2 relaxation times (T2-RT) are abnormal in opiate-dependent subjects.

Brain T2-RT is influenced by several factors including local deoxyhemoglobin content, which at steady state is proportional to cerebral blood volume (van Zijl et al., 1998). Because steady-state cerebral blood volume correlates with cerebral blood flow and metabolism (Grubb et al., 1974), steady-state T2-RT can be viewed as a surrogate marker for, and inversely correlated with, cerebral blood volume and metabolism. Inverse relationships between T2-RT and cerebral blood volume have been previously demonstrated (Anderson et al., 2000) and, using T2 relaxation time