Increased frontal lobe phosphocreatine levels observed in heavy cocaine users after treatment for cocaine dependence – An $^1$H MRS $T_2$ relaxometry study


Abstract. We have recently reported that relative concentrations of phosphocreatine (PCr) and creatine (Cr) may be estimated from brain $^1$H MR spectra based upon $T_2$ relaxation times. Emission tomography studies have consistently associated cocaine dependence and abstinence with decreased cerebral metabolism. We hypothesized that increased frontal lobe PCr levels would accompany treatment for cocaine dependence. Twenty-four cocaine dependent (CD) subjects were studied before and after 8 weeks of cocaine dependence treatment. Nine comparison subjects were studied at the same time points. At baseline, left frontal lobe ratios of PCr/Cr were $0.406 \pm 0.081$ in CD subjects and $0.411 \pm 0.016$ in comparison subjects. After treatment, these ratios increased 14.3% ($0.464 \pm 0.006$; $p = 0.006$) in CD subjects, remaining unchanged in comparison subjects (2.9%, $0.399 \pm 0.011$; $p = 0.480$). At baseline, PCr levels of non-responders were 17.8% lower ($0.375 \pm 0.042$) than those of responders, defined as 25% decrease in urine cocaine metabolites. After treatment, CD subjects had increased PCr levels: 18.4% ($0.444 \pm 0.035$; $p = 0.092$) for non-responders and 10.4% ($0.488 \pm 0.442$; $p = 0.092$) for responders. These results are consistent with decreased cerebral metabolism during treatment, measured as increased PCr. This is the first report using $^1$H MRS $T_2$ relaxometry to measure a change in human brain energetics.

1. Introduction

Phosphocreatine (PCr) and creatine (Cr) are important molecules in cerebral bioenergetics. The proton ($^1$H) magnetic resonance spectroscopy (MRS) creatine resonance at 3.0 ppm arises from both PCr and Cr. The relative concentrations of PCr and Cr may vary depending on cerebral metabolic status [6,15–17, 19,24,27]. For example, during photic stimulation, phosphorus – (31P) MRS has been used to document decreases in occipital cortex PCr levels [12–14,23,26].

The effects of chronic cocaine abuse on human brain metabolites are not well understood. Volkow [30] and Wang [31] reported increases in cerebral metabolism during active cocaine use and craving for cocaine. Animal studies have also reported a decrease in PCr, consistent with increased metabolism, following injection of cocaine in rat brain [2]. No change in $^1$H MRS Cr levels has been reported following...
acute cocaine administration in human subjects [5]. A number of investigators have reported increases
in $^{1}$H MRS brain creatine resonance intensity $[4,22]$ in cocaine users, which could explain the reported
lower ratio of N-acetyl aspartate (NAA) to creatine $[3,18]$ in some cocaine users. These observations sug-
gest that cocaine’s effect on cerebral metabolism and on PCR level is time dependent $[28]$ and additional
studies are needed to further understanding of cocaine’s effects on neurochemical markers.

Proton MRS is potentially a much more sensitive method for measuring changes in brain creatine
stores in vivo than $^{31}$P MRS. However, signals originating from PCR and Cr cannot be separated directly
because they have almost identical resonance frequencies in $^{1}$H MRS. We have recently demonstrated,
however, that PCR and Cr have markedly different $T_2$ relaxation times in vivo and, on this basis, their
relative concentrations may be estimated from $^{1}$H MR spectra $[14]$.

In this study, we collected 2D MRS data sets from cohorts of cocaine dependent ($N = 24$) and
non-cocaine using subjects ($N = 9$). The cocaine dependent subjects were assessed immediately prior
to and again following their participation in an eight-week, three arm, NIDA-sponsored treatment trial
examining the efficacy of venlafaxine, pramipexole, or placebo in reducing cocaine use. The comparison
subjects were assessed on two separate occasions separated by an eight-week interval. We hypothesized
that the cocaine dependent subjects would have lower levels of PCR at study entry and that these levels
would increase with treatment and reduction of cocaine use.

2. Methods

2.1. Clinical

All subjects provided written informed consent for a study that was approved by the Institutional
Review Boards of Boston Medical Center, McLean Hospital, and the Boston VA Healthcare System.
Eligible subjects were between 18 and 60 years of age. All cocaine dependent (CD) subjects were en-
rolled in a double blind, NIDA-sponsored, treatment study: three arm, placebo controlled assessment of
venlafaxine, or pramipexole as treatment of cocaine dependence (CREST II). All CD subjects met the
DSM-IV diagnosis of cocaine dependence and reported using cocaine on at least six occasions within the
28-day period prior to screening. Self-report of current cocaine use was substantiated with three urine
specimens that were positive for the cocaine metabolite benzoylecsomine (BE) (ng/ml) over a two week
period prior to study entry. Women with childbearing capacity were required to use an acceptable method
of birth control. Potential subjects were excluded if they had a current dependence on any psychoactive
drug other than cocaine, alcohol, or nicotine. In addition, those with neurological or psychiatric disor-
ders requiring immediate treatment or that would make medication compliance difficult were excluded.
Other reasons for exclusion included serious medical illness, current drug treatment, asthma, amenor-
rhea, due to pregnancy (by urine test), and abnormal lab results during screening. CD subjects with a
current history of alcohol dependence did not require medical detoxification.

Medical history, routine blood work, and physical examination, including vital signs and weight, were
obtained from all CD subjects as part of the CREST II trial. The following structured instruments were
used to evaluate the CD subjects: (1) Structured Clinical Interview for DSM-IV Axis I Disorders, Re-
search Version, Non-patient Edition (SCID-I/NP) obtained during the screening interview, (2) Addiction
Severity Index (ASI) obtained prior to randomization and after eight weeks of treatment, (3) A quanti-
tative urine toxicology screen for BE obtained three times a week during screening and throughout the
study.
MRI examinations were completed during active cocaine use prior to treatment and after 8-weeks of treatment. All CD subjects were randomized into one of three treatment cells: placebo, venlafaxine, or pramipexole. All treatment arms included manual-driven psychotherapy.

Comparison subjects were recruited by newspaper advertisement. A recruitment objective was to match the CD subjects on the basis of age, gender, and years of education. Comparison subjects had no Axis 1 diagnoses. Other exclusion criteria were similar to those employed for the CD subjects. The comparison group also completed two MRI examinations separated by the same time period as the CD subjects.

Response to treatment was assessed in two ways: by self-report (SR) and by urine toxicology report (UR). The response to treatment based on self-report of cocaine use was determined by the number of days cocaine was used in the last 30 days prior to treatment, as reported on the ASI and compared to the ASI Follow-Up Questionnaire after 8 weeks of treatment. A 25 percent drop in the number of days of reported cocaine use in a 30-day period was considered to be SR positive. All quantitative urine BE levels obtained the week prior to treatment were averaged, as were all quantitative urine BE levels after eight weeks of treatment. A twenty-five percent drop in mean urine BE levels from the first week to the last week was considered to be UR positive. These measures were chosen because they were temporally related to the scan acquisition.

2.2. Technical

A modified PRESS MRS sequence (Fig. 1) was implemented on a GE 1.5 Tesla SIGNA MR scanner at McLean Hospital to collect study data. Localized spectra were acquired from the left anterior frontal lobe with a voxel size of 18.75 cm$^3$ (2.5 × 2.5 × 3 cm$^3$; Fig. 2). Other scan parameters included: TR = 2.32 sec and 64 values of TE ranging from 48 msec to 678 msec. Each recorded FID had eight averages. Spectral bandwidth = 2000 Hz with 2048 data points.

After fully automated spectral processing, signal amplitudes for the 3.0 PPM creatine resonance were extracted from each spectrum at each of the 64 TE values (Fig. 3).

The Cre amplitude–TE curve obtained from each visit was fit to a mono-exponential model, as well as a bi-exponential model with PCr/tCr = 0.40 [7,9–11,25] initially for the $T_2$ values. Random permutations of the residues from the mono-exponential model were also fit to the bi-exponential model, in order to obtain non-parametric significance values for the goodness of fit [14]. Any results yielding significance
values greater than 0.02 were eliminated (Fig. 4). Only subjects with both visits meeting this significance criterion were included.

From the models, $T_2$ values were obtained for PCr from all the control subjects, and the median was calculated; the same procedure was performed for Cr. These values were in turn used to estimate the relative concentrations of PCr and Cr for both groups. Overall, the PCr/tCr ratios obtained were similar to the 0.40 value employed in the initial bi-exponential fits, lending confidence to this starting value. We employed this procedure because a full four-parameter fit, with the PCr/tCr ratio and both decay times variable, proved untenable given the available signal-to-noise ratio in the data.

3. Results

Comparison subjects and cocaine-dependent subjects were matched for gender, age and years of education. As expected, these two groups did not differ significantly for gender, age, or years of education (Table 1). In addition, cocaine-dependent subjects did not differ from comparison subjects in years of alcohol use (Table 1).

$T_2$ relaxation decay curves for the Cr resonance at 3.0 ppm both for cocaine-dependent and comparison subjects clearly demonstrated a bi-exponential decay characteristic for most subjects ($T_{2PCr} = 116 \pm 17$ msec, $T_{2Cr} = 338 \pm 19$ msec) in comparison with the results using a mono exponential fit.
Table 1
Baseline sample characteristics of comparison subjects and cocaine-dependent subjects

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Comparison subjects</th>
<th>Cocaine dependent subjects</th>
<th>All cocaine subjects versus comparison subjects</th>
<th>Cocaine nonresponders versus responders</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 9</td>
<td>Nonresponders (N = 13)</td>
<td>Responders (N = 11)</td>
<td></td>
</tr>
<tr>
<td>Females</td>
<td>5 56</td>
<td>4 30.8</td>
<td>3 27.3</td>
<td>1.97 0.161 0.035 0.851</td>
</tr>
<tr>
<td>Age (years)</td>
<td>42.44 4.22</td>
<td>40.85 6.47</td>
<td>47.82 6.16</td>
<td>0.394 0.535 7.23 0.013*</td>
</tr>
<tr>
<td>Years education</td>
<td>13.17 0.83</td>
<td>12.48 2.26</td>
<td>12.67 1.30</td>
<td>0.868 0.359 0.064 0.803</td>
</tr>
<tr>
<td>Weight</td>
<td>160.22 26.00</td>
<td>158.98 33.09</td>
<td>182.82 22.33</td>
<td>0.702 0.409 4.13 0.054</td>
</tr>
<tr>
<td>Drug spending</td>
<td>488.46 33.75</td>
<td>590.91 417.96</td>
<td>417.96</td>
<td>0.443 0.513</td>
</tr>
<tr>
<td>30 day cocaine use</td>
<td>20.08 9.41</td>
<td>9.41 17.91</td>
<td>9.17</td>
<td>0.324 0.575</td>
</tr>
<tr>
<td>Urine cocaine</td>
<td>10868 11499</td>
<td>51315 62477</td>
<td>51315</td>
<td>5.279 0.032*</td>
</tr>
<tr>
<td>30 day alcohol use</td>
<td>16.77 8.90</td>
<td>15.36 8.29</td>
<td>15.36</td>
<td>0.158 0.695</td>
</tr>
<tr>
<td>Years alcohol use</td>
<td>15.08 10.05</td>
<td>8.00 9.03</td>
<td>8.00</td>
<td>3.236 0.086</td>
</tr>
<tr>
<td>Years marijuana use</td>
<td>19.22 10.05</td>
<td>19.15 9.17</td>
<td>20.60 12.26</td>
<td>0.199 0.891 0.105 0.749</td>
</tr>
<tr>
<td>30 day marijuana use</td>
<td>6.92 8.60</td>
<td>5.36 6.44</td>
<td>5.36</td>
<td>0.245 0.626</td>
</tr>
<tr>
<td>Years heroin use</td>
<td>18.54 11.36</td>
<td>10.09 10.31</td>
<td>10.09</td>
<td>3.581 0.072</td>
</tr>
<tr>
<td>30 day heroin use</td>
<td>0.62 2.22</td>
<td>0.91 3.02</td>
<td>0.91</td>
<td>0.075 0.786</td>
</tr>
<tr>
<td>Years heroin use</td>
<td>1.69 4.11</td>
<td>3.18 8.50</td>
<td>3.18</td>
<td>0.315 0.581</td>
</tr>
<tr>
<td>Cigarettes per day</td>
<td>8.89 7.93</td>
<td>8.84 5.62</td>
<td>8.84</td>
<td>0.000 0.988</td>
</tr>
</tbody>
</table>
Estimated values for $T_{2PCr}$ and $T_{2Cr}$ were not significantly different between cocaine-dependent subjects and comparison subjects nor between their two visits.

At baseline, mean (SD) ratios of phosphocreatine to total creatine (PCr/tCr) were 0.406 (±0.081) and 0.411 (±0.016) in the cocaine-dependent and comparison subjects, respectively ($F = 0.037$, $df = 31$, $p = 0.849$). After treatment, PCr/tCr ratios measured at visit 2 were 0.464 (±0.093) for cocaine-dependent subjects while this ratio for comparison subjects remained approximately the same, 0.399 (±0.036) ($F = 4.155$, $df = 31$, $p = 0.050$) (Table 2). The mean changes in PCr/tCr after treatment were +14.3% ($p = 0.006$) in cocaine-dependent subjects and −2.9% ($p = 0.480$) for the comparison subjects.

Furthermore, when cocaine-dependent subjects were divided into responder/non-responder groups based on urine drug measures, the PCr levels of non-responders at both baseline and after treatment were lower than corresponding values of responders. At baseline responders and non-responders differed significantly in age (47.82 and 40.85 years, respectively; $p = 0.013$) and urine cocaine measures (51315 and 10868 urine benzoylecsmone, respectively; $p = 0.032$). A trend also existed for responders to have reported fewer days of alcohol use in the previous 30 days than non-responders (8.00 and 15.08 days, respectively; $p = 0.086$). Other baseline characteristics of comparison subjects and cocaine dependant responders and non-responders are summarized in Table 1.
Table 3

<table>
<thead>
<tr>
<th>Treatment medication (N)</th>
<th>Mean-increase</th>
<th>t-value</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pramipexole (8)</td>
<td>+0.076</td>
<td>1.692</td>
<td>0.135</td>
</tr>
<tr>
<td>Venlafaxine (9)</td>
<td>+0.062</td>
<td>2.411</td>
<td>0.042*</td>
</tr>
<tr>
<td>Placebo (7)</td>
<td>+0.033</td>
<td>1.195</td>
<td>0.277</td>
</tr>
</tbody>
</table>

PCr levels of both non-responders and responders increased after treatment (Table 2). Increased levels of PCr were accompanied by significant decreases in self-reported cocaine use for both non-responders and responders. At both timepoints, non-responders reported greater use of alcohol than responders, reaching significance after treatment ($F = 8.634$, $p = 0.008$). Non-responders were also significantly more likely to have current or past alcohol dependence or abuse than responders ($\chi^2 = 4.033$, $p = 0.045$). In addition, cocaine dependent subjects reported decreased alcohol consumption following treatment ($t = 2.187$, $p = 0.039$).

By dividing the patients into three treatment groups, there was a clear trend for increased PCr levels, consistent with a decrease in cerebral metabolism, associated with active medications used in treatment (Table 3). This increase in PCr levels for cocaine dependent subjects after pharmacotherapy suggests that treatment for cocaine dependence is associated with a decrease in cerebral metabolic rate, which may partly be due to a reduction in cocaine use.

4. Conclusion

Across our study sample, treatment for cocaine dependence appears to increase frontal lobe phosphocreatine levels by approximately 14% and non-responding cocaine users had lower baseline PCr levels than those of responding cocaine users. These findings are consistent with reports that cerebral metabolism decreases over time during abstinence [22,27,28]. In addition, this finding of increased PCr in left anterior frontal lobe is also consistent with decreased glucose metabolism in various frontal regions of past cocaine abusers [29]. As responders and non-responders reported decreased cocaine use after treatment, the increase in PCr seen in both groups could be partially attributed to decreased cocaine use.

The lower baseline levels of PCr in non-responders may partially be explained by higher alcohol consumption and a greater likelihood of suffering from past or current alcohol abuse or dependence. This is consistent with the report that chronic alcohol abuse in humans has been shown to decrease PCr as measured by $^{31}$P MRS [21]. Alcohol consumption has also been shown to decrease PCr levels in rat brain, $in vivo$ and $in vitro$ [1,8]. As alcohol use is associated with decreased PCr, a decrease in alcohol consumption would be expected to result in increased PCr. Therefore, changes in self-reported alcohol use may have contributed to increased PCr in cocaine dependent subjects after treatment.

A preliminary assessment indicates that this increase was somewhat greater in subjects who were treated with either venlafaxine or pramipexole (Table 3). As responders and non-responders had similar percentage increases in PCr levels after treatment, and both groups observed decreased use of both alcohol and cocaine, differences in PCr may be attributable to these changes in substance abuse patterns. However, relative lower PCr concentrations of non-responders in comparison with responders were observed both at baseline and after treatment (Table 2).
As cocaine-dependent responders were significantly older than non-responders, it is possible that this difference in age may have contributed to the difference in PCr between the two groups. However, Longo et al. have shown that the intensity of the PCr resonance, as assessed by $^{31}$P MRS, changed about 20% of the course of 60 years of normal aging [20]. Therefore, it is unlikely that this age difference of 6.98 years would have contributed significantly to the differences in PCr between responders and non-responders.

To the best of our knowledge, this is the first report involving the use of $^1$H MRS $T_2$ relaxometry to measure a change in human brain energetics. The increased magnetic resonance sensitivity of the $^1$H nucleus, relative to the $^{31}$P nucleus, allows the assessment of relatively small brain regions. However, the temporal resolution of the method is limited by the need to fit a sufficient number of TE values for reliable bi-exponential fitting.

**Acknowledgements**

This study was supported, in part, by grants from the National Institute of Drug Abuse (DA09448 and DA14178 to PFR, DA50038 to DAC); Career Development Award CCS.

**References**


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