Brain 31P-MRS at 4.0 Tesla: Methadone-maintenance therapy for opiate addiction

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Abstract: Phosphorus magnetic resonance spectroscopic imaging (31P-MRSI) at 4T was used to examine brain abnormalities in opiate-dependent subjects in methadone-maintenance treatment (MMT). Two cohorts were assessed, new intakes (N=12) scanned at the beginning of MMT, 5 of whom were rescanned after 2 months of MMT, and a second group (N=8) stabilized in treatment for 2 years, that served as a comparison group. Higher NTP levels were seen in the right and left frontal-lobes of the new intake MMT group (p=0.025) as well as higher b-NTP levels in the right frontal-lobe (p=0.004) in the new intake group, compared to the 2 year MMT treatment group. Total NTP levels were elevated (p=0.036) in a sub-cohort of the new intake group after 2 months of MMT compared to baseline levels. These metabolite differences and changes may reflect bioenergetic changes that occur during the transition between opiate dependence and methadone maintenance.

Introduction: Cerebral phosphorus metabolite abnormalities have been detected in prior 1.5 T 31P-MRS studies of opiate-dependent polydrug users at different stages of methadone maintenance treatment (MMT) (1, 2). However, the limited spatial resolution of those studies precluded anatomical assignment of metabolite abnormalities. Presently, we acquired frontal lobe 31P-MRSI data at 4 Tesla taking advantage of increased signal-to-noise and spatial/spectral resolution, to determine whether this brain area is selectively affected by chronic opiate abuse and methadone treatment. This region was selected because it exhibits gray matter NAA reductions in long-term heroin users (3) and structural abnormalities in short-term abstinent opiate abusers (4).

Methods: Opiate-dependent subjects were recruited from the Habit Management Institute in Boston, MA and provided informed consent to participate in these studies. Participants included new-intake subjects beginning MMT (age: 35.0±7.3yrs, 9 men, 3 women) and subjects stabilized in MMT for 2 years (age: 44.1±10.0yrs, 5 men, 4 women). Subjects were screened for recent illicit drug and alcohol use as well as for electronic/metallic implants prior to scanning. Women were screened for pregnancy. All data were collected on a Varian/UnityINOVA 4 Tesla (T) whole-body MR scanner at McLean Hospital. Orthogonal (sagittal, coronal, axial) localizer images were acquired with a rapid 2D gradient-recalled echo imaging sequence (slice thickness=5mm, FOV=24cm, matrix size=128x256) to identify initial positioning and, in subjects scanned serially, for confirmation of consistent positioning and slab placement across scans. High-resolution T_1 and T_2-weighted axial image sets (TE/TR=6.2/11.4ms, field-of-view (FOV)=24x24x16cm, readout-duration=4ms, receive bandwidth= ±32kHz, data matrix size=128x256x32, in-plane resolution=0.94x1.88mm, slice thickness=5mm, readout points=512, flip-angle=11/32°) were collected with a 3D-FLASH sequence for post-acquisition voxel placement and partial-volume analysis. A 2D-MRSI, pulse-acquire sequence (5) was used to acquire ^{31}P-MRSI data from a 3cm thick axial slab through the basal ganglia and frontal cortex (matrix size=8x8, TR=3s; tip-angle=80°; Rx bandwidth=±2 kHz; complex-points=1024; readout duration=256ms; NEX=4; pre-acquisition delay=1.2ms; field of view (FOV)=24x24cm; nominal volume=27ml, scan-time=13min). A slab spectrum using identical parameters except no phase-encodes (NEX=64, scan-time=3min) also was acquired. Spectroscopic imaging data were filtered and Fourier-transformed to localize spectra. Two spectral sets were analyzed for all subjects: left, right and summed frontal-cortex spectra, and whole-slab spectra. Metabolite peak areas were obtained using an iterative, time-domain fitting routine with prior knowledge. Mann-Whitney U-tests were used to test for group metabolite differences (new-intake vs. MMT stabilized) and repeated measures ANOVA was used to test for treatment duration effects (baseline vs. 2 months treatment).

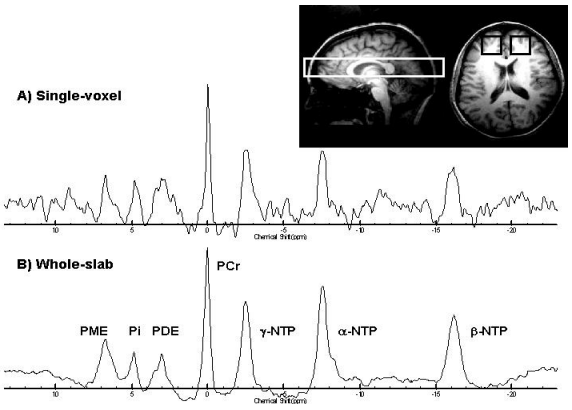

Figure 1 – Above: Phosphorus spectra from a 27cc voxel in the right frontal cortex (A) and a 3cm thick slab (B) in the brain of a 2-year MMT subject.

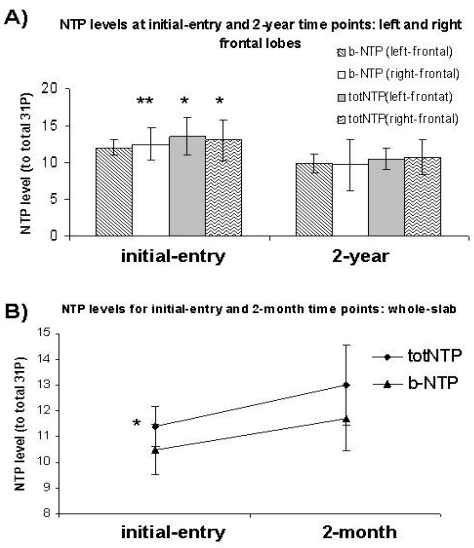

Figure 2 – Right: Beta and total-NTP levels in frontal cortex (A), and in slab (B) for initial-entry, 2 month and 2 year time points. Error bars represent standard error of the mean. (* p<0.05, **p<0.01)

Results/Discussion: Lower NTP levels were seen in the right and left frontal-lobes of the 2-year MMT group (p=0.025) as well as lower b-NTP levels in the right frontal-lobe (p=0.004) in the 2-year group(n=8), compared to the initial-entry MMT group(n=12) (figure 2-A). Total NTP levels are elevated in a sub-cohort of the initial-entry group (p=0.036, n=5) after 2 months of MMT (figure 2-B). These results are consistent with our prior whole brain findings at 1.5 T (1, 2) indicating bioenergetic metabolite differences during MMT and may reflect shifts in frontal lobe brain energy metabolism during early treatment that normalize with prolonged MMT. As heroin is more potent than methadone in reducing blood oxygen levels, presumably as a result of greater respiratory depressant effects (6), the transition between heroin abuse and methadone substitution could be accompanied by brain oxygenation increases that could alter bioenergetics. Additional studies are underway to characterize a more complete time course for metabolite changes in MMT subjects.

Conclusions: Heroin dependence appears to promote frontal lobe bioenergetics abnormalities. MMT may be associated with a shift in frontal lobe bioenergetics that may result from systemic oxygenation changes associated with the transition from heroin abuse to methadone maintenance.

References:

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