Lower Glutathione Levels in Methamphetamine Users

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Introduction: Methamphetamine (Meth) is a widely abused stimulant drug. Neurotoxicity associated with Meth may be partly mediated by oxidative stress[1,2], possibly related to astrogliosis.[3] Postmortem brain tissue from Meth subjects showed that brain regions with the greatest dopaminergic neuron loss also had decreased glutathione (GSH) levels, a major antioxidant.[4] However, no prior studies have evaluated *in vivo* GSH levels in the human brain of Meth users. Therefore, the aim of this study was to determine whether Meth users have altered brain GSH concentrations, using edited proton magnetic resonance spectroscopy (^{1}H MRS).

Methods: Twenty-four formerly Meth-dependent subjects (37.9±8.6 year old, range 22-54, 2 females) and 23 non-drug user controls (38.6±11.0 y.o., 19-55, 3 females) were studied with ^{1}H MRS. Informed consent was obtained from all participants. All subjects underwent a battery of neuropsychological tests for detecting cognitive deficits in seven cognitive domains[5]. MR studies were performed on a Siemens TIM Trio 3.0T system. A sagittal MP-RAGE scan (TR/TE/TI=2200/4.11/1000ms, 160 slices) was acquired and re-sliced into orthogonal directions to aid in voxel placement. A 27cc voxel was place in the posterior parietal gray matter (Figure 1) and spectra were collected using MEGA-PRESS to reveal the 2.95 ppm glutathione resonance (TR/TE1,2 = 1500/78,135ms, editing/control frequency: 4.56/7.50ppm, 6 x 64 averages, 6 x 6.5 min).[6] Data were processed offline in IDL with each spectrum adjusted to null out the 2.03 ppm NAA resonance. The resulting difference spectra were summed and processed in LC Model[7] to determine the GSH/NAA ratio. This value was multiplied by the NAA concentration calculated from a separate unedited PRESS spectrum (TR/TE= 3000/35ms, 64 averages of the parietal gray matter).

Results: The Meth group averaged 2,960±3,000g lifetime usage of Meth and had been abstinent for 90±65 days prior to the study. GSH levels were 12% lower in the Meth users compared to controls (GSH_M =0.94±0.14mM, GSH_C=1.06±0.13mM; p=0.003, Figure 3). GSH levels did not change with age across subjects, or with lifetime Meth usage or length of abstinence in the drug user group. In addition, GSH levels did not correlate with glutamate, a precursor for GSH, and neither NAA nor glutamate levels were different in this brain region between the Meth and control subjects. GSH levels also did not correlate with any of the neuropsychological tests.

Discussion: Long term abuse of Meth leads to neuronal damage throughout the brain via several mechanisms, one of which is oxidative stress.[8] These findings suggest a reduced anti-oxidant capacity in the Meth users, which may render them more vulnerable to oxidative stress if they have other co-morbid conditions that might enhance oxidative stress. The relatively modest decrease in GSH measured may not be severe enough for neurotoxicity to occur in this brain region since we did not observe decreased neuronal marker NAA or glutamate, a precursor of GSH. In conclusion, lower glutathione levels in the methamphetamine users suggest lower antioxidant capacity which may render these individuals more susceptible to other conditions that would cause oxidative stress. Future studies need to evaluate other brain regions and perform more detailed correlations with cognitive performance.

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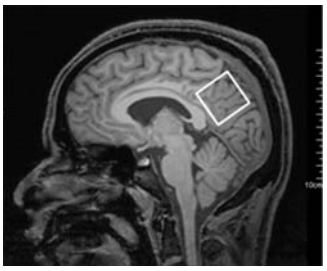

Figure 1: Sagittal MP-RAGE showing voxel placement

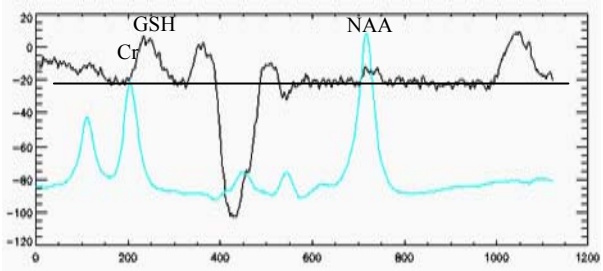

Figure 2: Panel display shows F1 spectrum (blue) and F1-F2 difference spectrum (black, 20x).

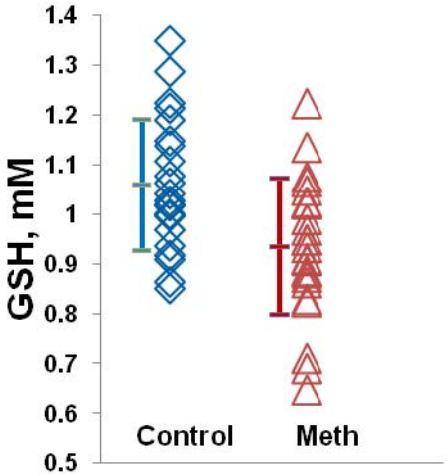

Figure 3

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