Anterior Cingulate Glutamate is Greater During Low Relative to High Dose Methadone Maintenance Dose in Heroin-Dependent Volunteers

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INTRODUCTION:

Dependence on heroin is a chronic, relapsing disorder for affected individuals and constitutes a major public health problem. Methadone is an FDA-approved, "gold-standard" medication for treating heroin dependence. Methadone, which is given orally once daily, can be highly effective for many individuals in replacing the effects of heroin, minimizing opioid withdrawal discomfort and reducing illegal opioid use.

Methadone is a full agonist at *mu*-opioid receptors, which are widely distributed in the brain and mediate both addictive and therapeutic (e.g. analgesic) effects of opioids. *Mu*-receptors influence glutamate (GLU) function through dual pathways (direct: located on pre-synaptic GLU terminals; and indirect: via effects on dopamine release), and opioid tolerance and physical dependence are associated with GLU neuroadaptations. Preclinical studies have shown that: (1) exposure to *mu*-agonists, e.g. morphine, decreases extracellular GLU in the anterior cingulate cortex (ACC), ventral striatum, thalamus, and hippocampus; and (2) during opioid withdrawal, GLU increases in these regions as well as the ventral tegmental area and locus coeruleus (Hao et al. 2005; Manzoni & Williams 1999; Pothos et al. 1991; Rada et al. 1991; Sepulveda et al. 1998; Xiang et al. 2006).

This ongoing study is determining whether manipulation of methadone maintenance dose in heroin-dependent subjects alters GLU levels in the ACC and thalamus using high-field short TE single-voxel ^{1}H spectroscopy, and whether this correlates with heroin craving and opioid withdrawal symptoms (within-subject comparison).

METHODS:

Heroin-dependent subjects without other psychiatric disorders or medical conditions (5 males and 1 female to date: mean age 44 ± 7 yrs, range 35-51 yrs) are first stabilized on high-dose methadone (100 mg/day) then admitted to an inpatient unit 3 days prior to the first MR scan (which begins 1 hr after the daily dose). Heroin craving, opioid symptoms, mood, and vital signs are also measured during the inpatient stay. After the first MR scan, subjects are discharged and the methadone dose is tapered and stabilized at a low level [first cohort, n=5 (4 males, 1 female; mean age 43 ± 6 yrs) at 25 mg/day; and current cohort so far, one 51 yr old male at 10 mg/day], and the inpatient stay and MR scanning are repeated about 1 month post initial scan.

The MR scanning was conducted on a 4 Tesla Bruker MedSpec whole body MR imager. A set of sagittal anatomical T_1-weighted images were collected, re-sampled and used to determine the ^{1}H spectroscopy voxel placement in the midline ACC and thalamus (2.0x1.5x1.5cm^3). Single-voxel suppressed- and unsuppressed-water ^{1}H spectra were collected using the following acquisition parameters: PRESS sequence; TE= 22ms and TR= 4.0sec; data points= 2,048 and bandwidth= 2kHz; 16 averages and 8 measurements (TR= 10sec, 4 averages and 1 water-unsuppressed measurement). The individual measures in each region were frequency- and phase- corrected prior to averaging to improve spectral resolution and S/N. The LC Model software package was used to quantify the ^{1}H metabolites [NAA, GLU, glutamine, *myo*-inositol, GPC+PC, PCr+Cr, taurine, alanine, aspartate, gamma-amino-butyric acid, glucose, *scyllo*-inositol, lactate and NAAG] as well as lipid and macromolecule resonances. Using the unsuppressed water signal, metabolite levels were expressed as mmol/kg wet weight. At 4 Tesla, the reliable quantified metabolites, NAA, GLU, *myo*-inositol, GPC+PC and PCr+Cr, were used in the statistical analysis. Two-way Dose (high, low) X Region (ACC, thalamus) ANOVAs were conducted using SPSS v.13, with simple effects tests as warranted.

RESULTS:

As shown in the figure, all 6 completers to date show lower GLU in the ACC during high- vs. low-dose methadone, yielding a significant mean change (simple effect p< .05), but not in thalamus (not shown; simple effect p= .77), Dose X Region $F(1,5)$= 14.24, p< .02. High-dose GLU level tends to correlate with less GLU change during methadone dose reduction, r= –.78, p< .07; the one female showed the highest initial GLU level and least dose-related change. Other metabolites do not presently show significant changes. Mean heroin craving across inpatient days tends to be lower during high-dose methadone (p= .07), and craving during high-dose methadone is positively correlated with change in ACC GLU during methadone dose reduction, r= +.85, p< .04. Opioid withdrawal symptom levels are presently mild (which led to our reducing the low maintenance dose in the current cohort) and not correlated with GLU.

QuickTime™ and a
TIFF (LZW) decompressor
are needed to see this picture.

DISCUSSION AND CONCLUSION:

These novel data in humans, which are consistent with preclinical results, show that GLU concentrations are associated with opioid dependence level. As control group data accrue (i.e., matched for age, gender and cigarette smoking), we will determine whether high-dose methadone GLU levels are decreased or, alternatively, whether low-dose methadone GLU levels are increased relative to levels of healthy control. These preliminary findings suggest that GLU variations could be an endophenotype for opioid dependence state, and that elevated craving during high-dose methadone (perhaps reflecting poor medication response) could predict GLU change. These data also suggest that antiglutamatergic medications could be useful for treatment.

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