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Methadone maintenance dose modulates anterior cingulate glutamate levels in heroin-dependent individuals: A preliminary *in vivo* ^{1}H MRS study

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ABSTRACT

Mu-opioid receptor agonists alter brain glutamate (GLU) levels in laboratory animals. This clinical study used proton magnetic resonance spectroscopy (^{1}H MRS) to examine regional brain GLU levels during experimental manipulation of methadone (MTD) maintenance dose under double-blind, within-subject conditions in seven heroin-dependent volunteers. Subjects were scanned first at a high MTD dose (100 mg/day), underwent a 3-week outpatient MTD dose taper, and then were scanned again at a low MTD dose (10–25 mg/day; modified for participant comfort). Five age- and cigarette smoking-matched controls were scanned once. *In vivo* short echo time (TE=22 ms), single voxel ^{1}H MRS data from midline pregenual anterior cingulate cortex (ACC) and thalamus (4.5 cm^{3} each) were collected using PRESS on a 4-Tesla MRI system. Absolute metabolite levels were quantified. GLU levels in the ACC, but not the thalamus, were higher at the low relative to the high MTD dose in heroin-dependent subjects. No other metabolites differed by MTD dose, or between control *vs.* heroin-dependent subjects (at either MTD dose). GLU levels in the ACC were inversely related to the duration of cigarette smoking (controls) and heroin use (experimental group). Future studies are warranted to investigate the relationship between GLU levels during treatment (and detoxification), and withdrawal symptoms or relapse.

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1. Introduction

Glutamate (GLU) neurotransmission is fundamental to human brain function. Indeed, 80–90% of all cortical neurons/synapses are glutamatergic (Rothman et al., 2003; Hyder et al., 2013). At rest, 60–80% of brain energy consumption (oxidative glucose metabolism) is related to GLU activity (Rothman et al., 2003). Clinical proton magnetic resonance spectroscopy (^{1}H MRS) can reliably and precisely measure *in vivo* GLU levels at anatomically relevant volumes in cortical (*e.g.*, pregenual anterior cingulate) and subcortical regions (*e.g.*, thalamus) at magnetic field strengths of 3 T (T) and above.

Chronic opioid (*e.g.*, heroin, methadone; mu opioid receptor [MOR] agonizts) use is associated with altered neuronal network activity (for review, see Goldstein and Volkow, 2011), glucose metabolism (Galynker et al., 2000, 2007), and lower dorsal anterior cingulate cortex (ACC) glutamate/glutamine (GLX) levels compared with matched controls (Yücel et al., 2007; Verdejo-García et al., 2013). Experimental preclinical studies demonstrated that chronic morphine administration *decreases* GLU levels in several brain regions, including the prefrontal cortex (PFC), ACC, hippocampus and thalamus, either directly *via* MORs located on presynaptic GLU neurons (Nicol et al., 1996; Meldrum, 1998; Sepulveda et al., 1998; Ostermeier et al., 2000; Vogt et al., 2001; Hao et al., 2005; Xiang et al., 2006) and/or indirectly *via* dopamine modulation of GLU neurons (Pothos et al., 1991; Rada et al., 1991; Yamamoto and Davy, 1992). Conversely, MOR antagonists (*e.g.*, naloxone) *increase* GLU levels in the ACC, PFC, hippocampus, and locus coeruleus in animals (Huang et al., 1997; Manzoni and Williams, 1999; Sepulveda et al., 1998; Guo et al., 2005; Hao et al., 2005;, Sepulveda et al., 2004). Similarly, morphine discontinuation *increased* GLU levels in the PFC and hippocampus (Gao et al., 2007), but not the thalamus (Xiang et al., 2006), as measured with *ex vivo* ^{1}H MRS.

This pilot study used high-field (4 T), short-echo time (TE=22 ms), single-voxel ^{1}H MRS (Stanley et al., 2000) to measure

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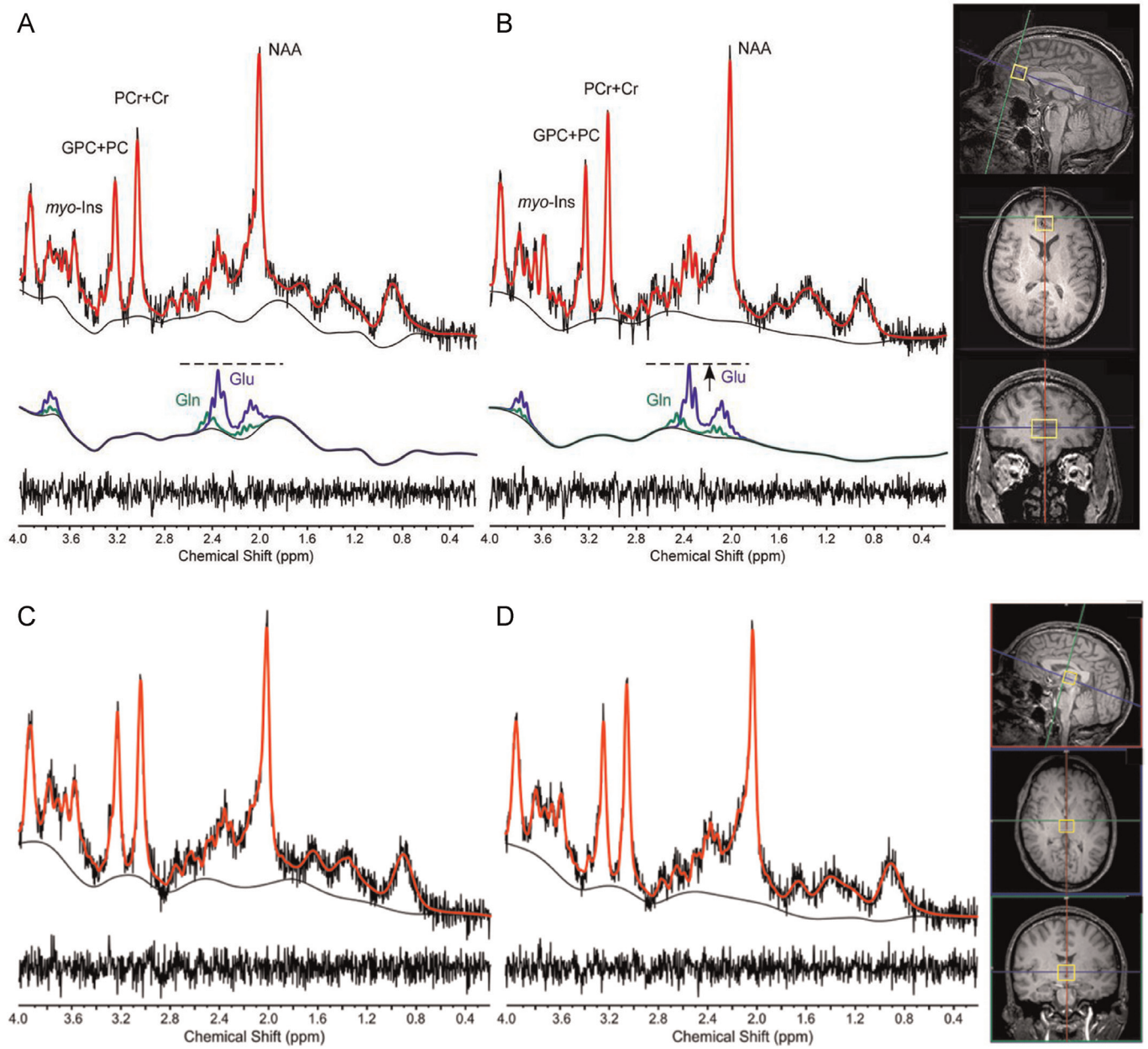

Fig. 1. *In vivo* ^{1}H spectrum measured in the midline pregenual ACC region of one subject during (A) high-dose (100 mg/day) and (B) low-dose (10–25 mg/day) methadone. Each methadone dose condition shows the modeled curve of the sum of metabolites (red) superimposed on the acquired spectrum, the individual curves for glutamate (GLU; blue), glutamine (GLN; green) and the residual of the fit. The dashed line is an amplitude reference. *In vivo* ^{1}H MRS spectrum measured in the thalamus of one subject during (C) high dose (100 mg/day) and (D) low dose (10–25 mg/day) methadone. Each methadone dose condition shows the modeled curve of the sum of metabolites (red) superimposed on the acquired spectrum. Images of the three-dimensional localization of each voxel on the MRI scan are depicted to the right of the upper (ACC) and lower (thalamus) panels. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

in vivo changes in brain regional GLU levels in heroin-dependent volunteers during initial high dose methadone (MTD) maintenance and subsequent dose reduction compared with non-heroin-using, cigarette-smoking, and age-matched controls. We hypothesized that MTD dose reduction would correspond with an increase in GLU levels in the ACC, but not the thalamus, consistent with the preclinical literature.

2. Methods

2.1. Subjects

The local Institutional Review Board approved all procedures. Volunteers (18–55 years old) with MRS, neurological, or cardiovascular contraindications were excluded. Substance use and psychiatric disorders were assessed using the Structured Clinical Interview for DSM-IV (SCID; First et al., 1996). Heroin-dependent subjects not seeking treatment who submitted an opioid-positive (>300 ng/ml; monitored and temperature-tested) urine sample (negative for benzodiazepines or barbiturates [<300 ng/ml] and cannabinoids [<50 ng/ml]) were invited to participate. Subjects were not excluded for cocaine metabolite-positive urine [≥ 300 ng/ml] at screening.

Current cigarette smokers (expired carbon monoxide verified) who did not currently use other substances (verified by urinalysis) and did not meet criteria for other psychiatric diagnoses were invited to participate as smoking-matched control subjects.

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