Double-blind, Placebo-Controlled, Dose-Response fMRI Trial of Buprenorphine: Differential Valence of BOLD Response Modulation to Innocuous and Noxious Stimuli in Sensory and Striatal Regions

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Introduction: Blood-oxygenation level dependent (BOLD) functional Magnetic Resonance Imaging (fMRI) has begun to be applied to probe how specific therapeutics modulate the acute central nervous system (CNS) response to noxious stimuli. Complementary to more traditional behavioral and pharmacokinetic/pharmacodynamic methods, BOLD fMRI provides information on neural systems differentially affected by drugs with different mechanisms and may be more sensitive than subjective ratings of perceived pain [1,2]. Buprenorphine (Buprenex) is a mixed opioid partial agonist and antagonist commonly used to treat opioid addiction, but has been shown to have both analgesic and antihyperalgesic effects in healthy human subjects [3]. We characterized the effect of two doses of buprenorphine in modulating the CNS response to a paradigm battery (brush, von Frey and noxious heat) that stimulated both mechanical and thermal receptors and provided both innocuous and noxious stimulation. This design enabled the drug effect to be characterized as a function of differential somatosensory stimuli as well as brain region.

Methods: 24 right-handed, healthy male subjects participated in this study. Each subject underwent both placebo and Buprenorphine scanning sessions separated by ~14 days, with 12 receiving the low dose (0.1 mg/70kg) and 12 receiving the high dose (0.2 mg/70kg) of the drug. Buprenorphine or placebo (physiological saline) were infused intravenously approx. 20min prior to the fMRI paradigm battery. In each dose cohort, 6 subjects received placebo first and 6 received Buprenorphine first. fMRI data were collected on a 3T Siemens Trio Scanner. fMRI parameters: fMRI data were collected using a gradient echo-echo planar pulse sequence (GE-EPI) at a 3.5 x 3.5 x 3.5 mm^3 resolution. GE-EPI Parameters: TR = 2500 msecs, TE = 30 msecs, FOV = 224x224, FA = 90°, # of Slices = 41 axial slices and # of Volumes =122. Each subject underwent three functional runs where the dorsum of the subject's left foot was stimulated by a Velcro brush (innocuous stimulus), a von Frey filament (mildly noxious stimulus) and with heat (noxious stimulus). For the heat functional scans, the heat stimulus corresponded to a subject-specific threshold temperature. The average threshold temperature for 0.1 and 0.2 mg/70kg dose cohorts are 46.9 ± 0.7 °C and 46.4 ± 0.7 °C, respectively. All image preprocessing (coregistration, spatial smoothing, temporal filtering, etc) and GLM analysis was performed using FSL. Group-level results shown below were achieved using a mixed-effects paired comparison. Self-reported pain ratings were recorded simultaneously during fMRI.

Results: Brain structures of sensory/pain and opioid circuitry [1,2] were identified as being activated by all paradigms in the placebo condition, with a stronger response to the more noxious stimuli observed. Single subject BOLD timecourses in response to 6.65 mm filament von Frey stimulation from the foot region of contralateral S1 region are shown in Figure 1. The BOLD response corresponding to the saline condition is shown in red, while the traces representing the Buprenorphine condition are shown in blue, reflecting a dose-dependent attenuation of the BOLD fMRI signal by Buprenorphine. Of the three functional paradigms, brush, von Frey and heat, a reduction in self-reported pain ratings was observed for the heat stimulus at the high, but not the low, dose condition (Figure 2). The difference in the heat response for the saline conditions between low and high dose cohorts was not significant (p=0.22).

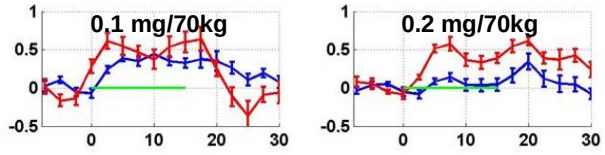

Figure 1: Peristimulus plots of response to von Frey (SI in placebo (red) and buprenorphine (blue) condition.

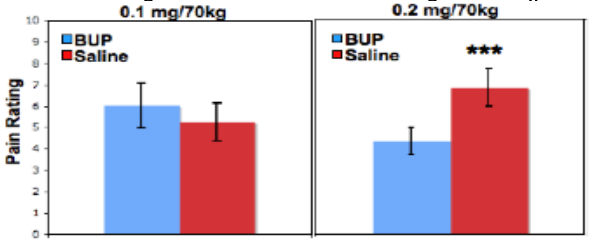

Figure 2. Pain Ratings for low and high dose Buprenorphine. ***p=0.03

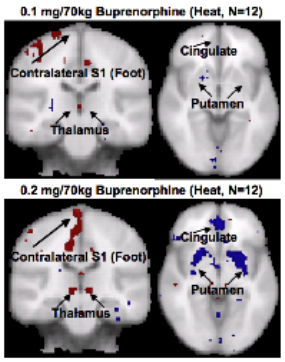

Figure 3: Dose response relation to CNS activation during heat stimulation.

Figure 3 depicts the group-level (N=12) paired comparison activation (z > 2.3) maps for heat stimulation in both doses of Buprenorphine. Neuronal structures demarcated in red (contralateral S1 and thalamus) correspond to regions having greater activation during the saline condition, while those structures in blue (cingulate and putamen) represent regions having greater activation for the Buprenorphine condition. The effects of the 0.2 mg/70kg dose of Buprenorphine are significant and more robust compared with the 0.1 mg/70kg dose. Group-level results for the von Frey stimulus revealed a similar dose-dependent modulatory effect; in contrast, there was little significant modulation of the CNS response to the brush paradigm (data not shown).

Discussion: This study demonstrated (1) a differential degree of drug modulation of CNS responses to innocuous vs. noxious stimuli, and (2), interestingly, a differential *valence* of modulation in striatal vs. sensory brain regions; the higher dose of Buprenorphine strongly attenuated the responses in somatosensory cortical and thalamic regions, but potentiated structures such as the putamen, amygdala and anterior cingulate cortex whilst eliciting a robust subjective analgesic effect. This finding may reflect the mixed pharmacology of buprenorphine (mu-opioid partial agonist/kappa-opioid antagonist), in contrast to opioid agonists previously studied using fMRI.

[1] Schweinhardt P. *et al.* (2006) *NMR Biomed.* **19** 702; [2] Borsook D. *et al.* (2007) *Drug Dev. Res.* **68** 23; [3] Zacny et al (1997) *Brain.* 122 (Pt 12) 2245.