Decreased Glutamate in the Periaqueductal Gray Associates with Neuropathic Pain

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Introduction

Glutamate is the major excitatory neurotransmitter in the human central nervous system (CNS) (Osikowicz et al. 2012). The periaqueductal gray (PAG) is a key component of descending pain modulatory system (DPMS) in the human CNS, with both inhibitory and excitatory outputs to the dorsal horn of the spinal cord via the rostroventral medulla that powerfully modulate nociceptive inputs. Increasingly from both animal and human studies, we recognise the relevance of the DPMS in the maintenance and modulation of neuropathic pain (De Felice et al. 2011). Here, we specifically assess the relationship between increased descending inhibition, as reflected by an increased excitatory glutamate level within the PAG, and the degree of neuropathic pain. We aim to quantify glutamate concentrations in the PAG, from healthy controls and neuromyelitis optica (NMO) patients, using ^{1}H MR spectroscopy (MRS). Neuromyelitis Optica (NMO) is a rare and devastating neurological condition that commonly features subacute longitudinally extensive demyelinating plaques in the spinal cord. NMO patients with these cord lesions often experience a severe and treatment resistant chronic pain syndrome (Kanamori et al. 2011).

Methods

18 NMO patients (4 males, age 51.9±14.3) and 17 healthy subjects (7 males, age 48.3±17.1) were included in this study. All MR measurements were carried out on a 3T Siemens Verio scanner using 12-channel head coil with 4-channel neck coil. A T1 MPRAGE (TR=2.3s, TE=3.59ms, flip angle 9°, voxel 1x1x0.9mm) was acquired to position the volume-of-interest (1x1x1cm) for MRS in the PAG. B0 shimming was achieved using GRE shim (Shah et al. 2009). A modified semi-LASER sequence (TE = 28 ms, TR = 3s, 192 averages) was used to acquire spectra from PAG (Oz et al. 2011). Spectra were processed in MATLAB and quantified with LCModel[5] with water scaling option using simulated basis spectra with a measured macromolecule spectrum. Only metabolites that were reliably quantified (Cramér-Rao lower bounds, CRLB ≤ 50% and correlation r > - 0.5) from at least half of the spectra were included in the final analysis. Metabolite concentrations were determined after correcting for T2 relaxation times, tissue water content and CSF contributions (determined by FAST segmentation in PAG). Neuropathic pain was assessed by the painDETECT, a questionnaire that ambiguates nociceptive pain from neuropathic (Freynhagen et al. 2006).

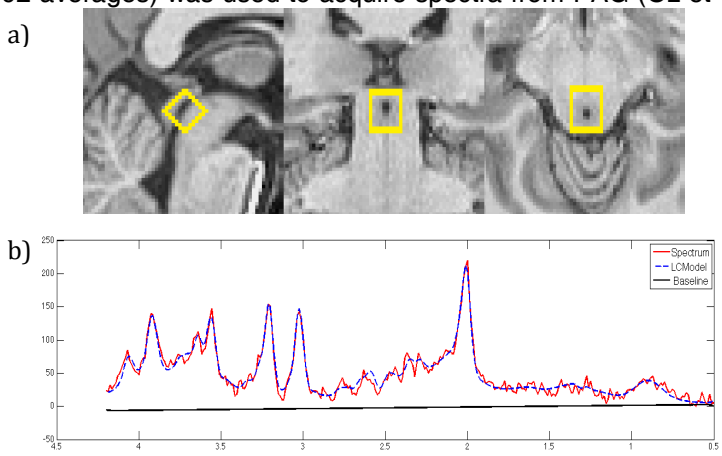

Figure 1. ^{1}H MR spectra obtained at 3T with semi-LASER from the PAG in one representative subject. a) 1cm^{3} voxel in PAG b) Spectra for LCModel fitting.

Results and discussion

Spectra with good SNR and spectral resolution were consistently obtained from both groups (Fig. 1). There were no significant differences between NMO and control groups, for all reliable metabolite concentrations, including tNAA (p=0.30), mIns (p=0.43), Creatine (p=0.82), tCho (p=0.23) and glutamate (0.11). Interestingly only glutamate was found to be negatively correlated to the degree of neuropathic pain (r=-0.57, p=0.013, Fig. 2). This likely indicates that with more glutamate there is more excitatory OFF cell activity in the PAG and more descending inhibition of nociception in the spinal cord, and consequently inhibition of aberrant NMO-lesion induced pain information, making these subjects less neuropathic. Our findings suggest that glutamate levels may reflect the tone of inhibitory activity established in the descending pain inhibition system. The exciting possibility of developing glutamate-enhancing PAG-targeted therapies for chronic pain conditions must await further carefully designed studies.

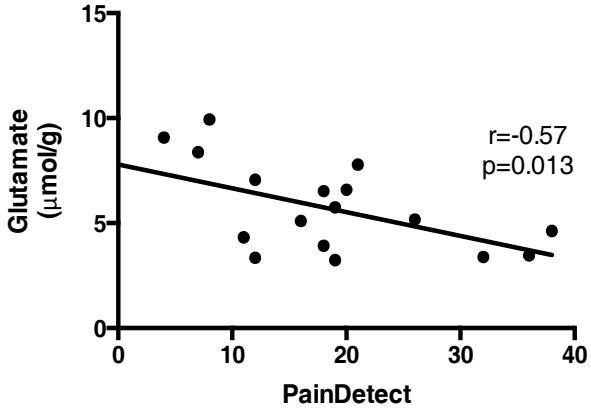

Figure 2. Glutamate negatively correlates to the degree of neuropathic pain for NMO patients.

References

De Felice et al. *Pain* 2011; Freynhagen et al. *Curr Med Res Opin*. 2006; Osikowicz et al. *Exp. Physio*. 2014; Kanamori et al. *Neurology* 2012; Oz et al. *MRM* 2011; Shah S., et al., ISMRM 2009, p.565.