THE ROLES OF PCR IN BRAIN ACTIVITY

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Background:

Activation of the brain increases energy use, and this is sustained by an increased glucose and oxygen supply delivered through a local increase in blood flow. As is well known, this haemodynamic response is protracted and delayed and during this initial delay it is possible that ATP generation may be insufficient to meet the instantaneous increase in energy demand. It is possible for phosphocreatine (PCr) to act as an energy buffer for the few seconds it takes to increase local oxygen supply, which makes sense in that the capacity of the PCr reserve to meet all cellular energy requirements is measured in seconds. If PCr acts as an energy buffer we would expect to see a decrease in PCr concentration accompanied by an increase in inorganic phosphate (P_i) and possibly a slight increase in pH (alkalosis) due to the absorption of a proton. However, there is an alternative hypothesis for the putative role of PCr in sustaining energy metabolism, namely the shuttle hypothesis[1] in which PCr is the vehicle by which high energy phosphate is conveyed from the site of production (the mitochondria) to the site(s) of its utilization. If energy demand increases there will be an increased requirement for PCr resulting in changes which are mirror images of those predicted by the energy buffer hypothesis. To investigate which, if any, of these hypotheses may be relevant during the onset of brain activity, image guided localized ^{31}P MRS was used at 3T to measure concentrations of high energy phosphate metabolites in the visual cortex during the first few seconds following onset of an intense visual stimulus.

Method:

Nine healthy volunteers participated in the study. Data were acquired on a Philips Achieva 3T system using a transmit/receive body coil for ^{1}H imaging and a ^{31}P surface coil for MRS. Initial BOLD fMRI experiments (TR=1.5s; resolution = 2x2x2mm^3) were performed in each subject using the body coil (with the ^{31}P coil in situ) to enable positioning of the MRS volume in the region of maximum activation. Visual stimulation was achieved using red LED goggles driven at 8Hz. Statistical parametric maps were calculated in real time using Philips IViewBOLD software. ^{31}P spectra were then acquired from a 35x35x35mm^3 volume encompassing the primary visual cortex positioned perpendicular to the calcarine fissure using ISIS localization with TR=30s, BW=3000Hz, samples = 2048. Acquisition of baseline and stimulation period spectra was interleaved, with a group of eight FID's with visual stimulus applied followed by a group of eight with no visual stimulus. In each acquisition period, the visual stimulus was applied at t=0 for 3s with data acquisition commencing at 3s. To maintain alertness, subjects were asked to respond to an auditory stimulus (applied at t=4s) with a button press. The scanner acquisitions were synchronised with the stimulus using an external trigger. For both the baseline and stimulation period, four spectra (32 acquisitions) were averaged and PCr and P_i concentrations and pH values analysed using the AMARES algorithm in jMRUI.

Results:

BOLD images showed strong responses to the visual stimulation in all volunteers. No significant changes in PCr ($p = 0.4$), P_i or pH were measurable between the baseline and stimulated periods for the individual volunteers. Individual spectra were therefore normalised to the PCr peak area at baseline and averaged together for stimulation and baseline periods. Analyses of the averaged spectra indicates an increase in PCr (7 ± 2 %) (Fig. 2), a decrease in P_i (20 ± 12%) and a decrease of pH towards a more acidic condition ($pH_{baseline}$ = 7.09±0.01, $pH_{stimulation}$ = 7.01±0.01) during the visual stimulation period.

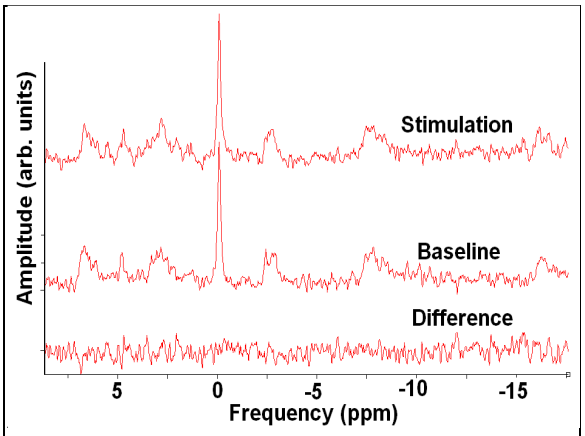

Figure 1: ^{31}P spectra, averaged across all subjects for both stimulation (top) and baseline (middle) periods.

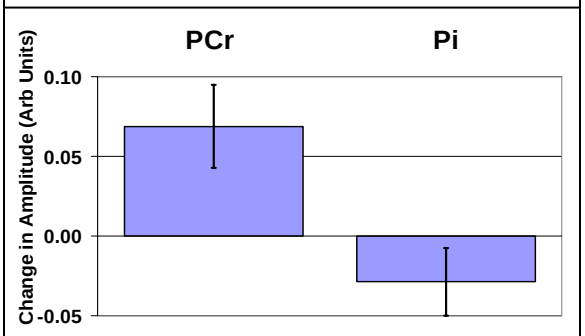

Figure 2: Graphs showing changes in metabolite levels (on – off) across all subjects

Discussion:

The changes observed on activation are small, and do not reach individual significance. However, their magnitude and direction (increase in PCr, decrease in P_i and small acidification) are consistent with an increase in shuttle activity but do not suggest a significant energy buffering role for PCr. There have been very few other reports of studies of changes in PCr during the initial period of brain activation, but our results are in contrast to those of Rango et al[2] who, using a surface coil at lower field (1.5T), to study the change in metabolite concentrations in the first few seconds of a visual stimulus. They observed a significant decrease in PCr levels (18.1±5.5%) but no change in pH in a subgroup of eight volunteers studied. Sappey-Marinier et al[3] used image guided localised spectroscopy to monitor changes in the visual cortex over four 6.4 minute blocks (stimulus OFF-ON-ON-OFF) and found that levels of PCr/Pi decreased significantly over the period of the photic stimulation with a slight increase in pH over the same period. The situation during sustained activation, when blood flow and nutrient supply have increased, is likely to be different from that in the early seconds of activation. A decrease in PCr is consistent with a possible increase in ADP levels which, though still low (below the detection threshold for ^{31}P MRS) could drive increased ATP production rates. Although no clear role for PCr in the brain has emerged, these results suggest it may be different during transient and sustained brain activity

References:

1. Meyer, R.A. et al, Am. Phys. Soc. (1984), C365. **2.** RANGO, M et al, (1997) *Mag Res Med*, 38(6), 878-883; **3.** SAPPEY-MARINIER, D. et al;, (1992) *J. Cereb. Blood Flow Metab*, 12(4), 584-592;