ENDOGENOUS CONTRAST APPROACH FOR MRS-BASED MOLECULAR IMAGING OF BRAIN TUMOURS

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Human brain tumours can be diagnosed non-invasively by Magnetic Resonance Imaging (MRI) with high Specificity, but Sensitivity needs improvement (Julià-Sapé et al 2006). Targeted or "smart" contrast agents and Magnetic Resonance Spectroscopy (MRS) may improve this in the near future. In this respect MRS-based Decision Support Systems (DSS) have been developed (Tate et al., 2006) and are freely accessible to interested clinical centres (**http://azizu.uab.es/INTERPRET/int_Disc_Proto.shtml**). Nevertheless, further development of MRS based methods to help clinicians to carry out improved diagnosis, prognosis and eventually therapy follow-up is hampered by the high number of brain tumour types (and more recently molecular subtypes). This makes a difficult task to acquire enough MRS compatible cases for classifier development of use in an evolving DSS. Furthermore, obvious ethical reasons usually restrict following the progression of human tumours once diagnosed. This problem is partially circumvented by using murine brain tumour models, mostly induced by stereotactic injection of established tumour cell lines. Additionally, genetically engineered mice (GEM) spontaneously developing tumours are presently available. We have been recently interested in developing strategies to increase the dynamic range of MRS pattern changes due to tumour type and progression in mice harboring brain tumours, for future translational applications in humans. Our working hypothesis has been that the perturbation of the tumour metabolome in a reversible way will produce MR-detectable spectral pattern changes which can be objectively recognized by pattern recognition tools and transformed into tumour types/subtypes. Moreover, this approach may also be used to generate images of the evolving tumour phenotype, due to progression or therapy response. For this, MRS pattern perturbation in high grade gliomas grown in C57BL/6 mice by sterotactic injection of GL261 cells was accomplished by induced acute hyperglycemia. Extracellular glucose accumulation was demonstrated in the tumour volume by single voxel (SV) MRS, but not in the surrounding brain parenquima, and the MRS pattern perturbation shown to be recognizable by a classifier. Furthermore, chemical shift imaging (CSI, also known as multivoxel, MV) was recorded from an additional set of animals allowing the heterogeneity of glucose accumulation inside the tumour to be imaged with a time resolution of ca. 20 min. (Simões et al. NMR 2008 a, b). This is summarized in the CSI of glucose accumulation shown in figure 1.

Future work will address how different murine tumour types and grades respond to defined metabolome perturbation strategies while complementary results with other molecular imaging strategies will be investigated.

References:

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Figures:

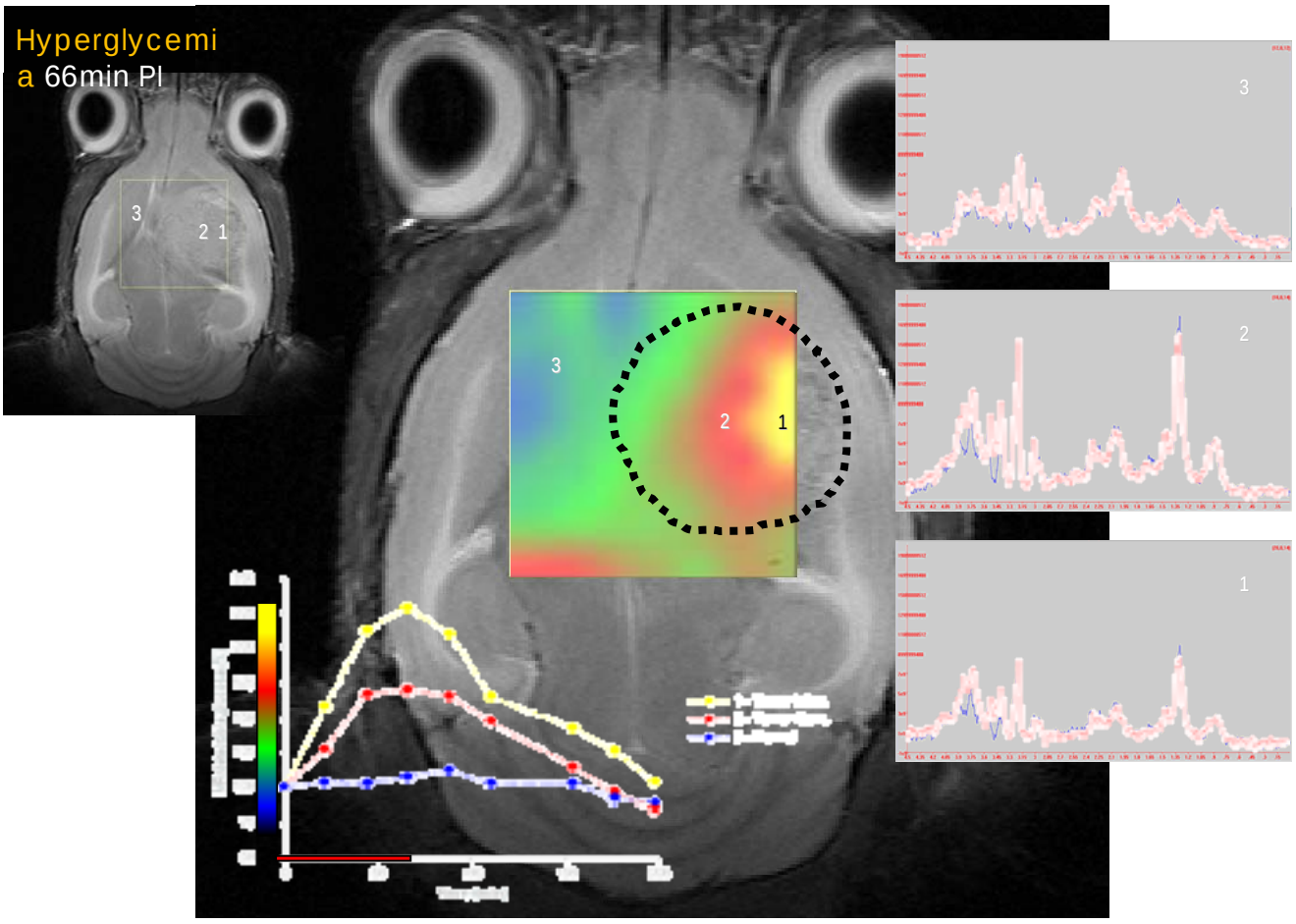

Figure 1. C57BL/6 mouse harbouring a GL261 high grade glial brain tumour studied with dynamic ^{1}H-CSI at 7T, following acute hyperglycemia (induced by intraperitoneal D-Glucose bolus: 25% in saline, 10µl/g). ^{1}H-CSI spectral grids were collected using: 2500/12 ms TR/TE, 21m30s total acquisition time. Each CSI grid was post-processed to quantify the relative brain MR-detectable glucose changes which were then displayed as colour-coded maps – the one shown here was collected at 66min post-injection of glucose. This was performed by comparing the 3.43 ppm peak intensities, as shown here (grey boxes at right) for spectra collected from the brain regions 1, 2 and 3 during euglycemia (spectra in blue) and at 66min of the hyperglycaemic period (spectra in red); time-course kinetics of brain MR-detectable glucose changes at these positions are also plotted in the lower part of the image (1, region of maximal glucose increase; 2, tumour centre region; 3, apparently normal or peritumoral brain region). The reference image of the CSI (T2-weighted) is displayed twice (in the centre and in the upper left) to allow a good visualization of normal brain parenchyma, the tumour and the position of the VOI (upper-left) as well as the glucose map (centre – tumour borders, black dotted line, manually highlighted).