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that the treatment with aspirin and 5-FU did not cause toxicity after 48 h exposure which may explain the lack of SSAT response to these drugs.

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Insulin-like growth factor binding protein-5 as a biomarker for the detection of early liver disease

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A steady upward trend in the mortality rates from cirrhosis in the UK has been observed in recent years and in particular in Scotland. The liver has a huge regenerative capacity but early diagnosis is essential. Non-alcoholic fatty liver disease (NAFLD) is the most common cause of liver disease in the developed world mirroring the global epidemic of Type 2 diabetes and obesity.

This work aims to determine if Insulin-like growth factor binding protein-5 (IGFBP-5) would be a suitable biomarker for the detection of NAFLD. It has already been shown to be upregulated in skin fibrosis (Yasuoka et al., 2006a) and in fibrosis of the lung (Yasuoka et al., 2006b). Also, its expression enhances the survival of hepatic stellate cells and myofibroblasts and the expression of profibrotic genes (Sokolovic et al., 2010)

The University of Edinburgh have developed a model of NAFLD in vitro using C3A cells (Filippi et al., 2004), a clonal derivative of the human hepatoblastoma-based HepG2 cell line. The model utilised two methods to induce lipid accumulation in cell lines. In the first, cells were treated with lactate, pyruvate, octanoate and NH₄Cl (LPON) for up to 7 days in culture, and this has been shown to increase intracellular reactive oxygen species (ROS). Alternatively, lipid accumulation can be induced, without ROS formation, by the presence of oleate. The lack of ROS formation has been suggested to be due to the inability of oleate to induce carnitine palmitoyltransferase-1 (CPT-1) which is essential for the transport of long chain fatty acids across the mitochondrial membrane for oxidation (Nakamura et al., 2009). In our experiments, intracellular lipid accumulation was observed by staining cultures with haematoxylin/oil red O, and IGFBP-5 release into the medium was measured using an ELISA.

Intracellular accumulation of lipids was observed to increase over time in culture with the presence of LPON or oleate in comparison with the controls. In the presence of LPON, IGFBP-5 increased to 0.3 ± 0.1 ng/ml at 7 days, whereas, in the presence of oleate, IGFBP-5 secreted increased to approximately 0.1 ng/ml at 5 and 7 days (Fig. 1). Control levels were below the levels of detection of the ELISA. The difference in levels of IGFBP-5 may be attributed to the lack of ROS formation with the presence of oleate. This suggests that IGFBP-5 may be a suitable biomarker for the detection of NAFLD.

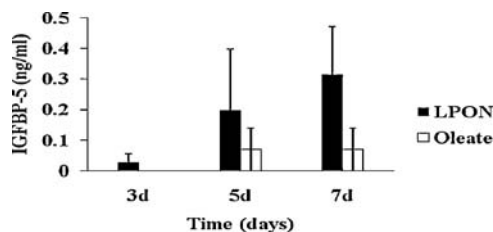


Fig. 1. IGFBP-5 release from C3a cells exposed to LPON or oleate (results are mean ± SEM, n = 3).

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Acute depletion of the prion protein may abrogate Aβ oligomer toxicity

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Amyloid-beta₁₋₄₂ (Aβ) oligomers bind to the prion protein (PrP) with very high affinity (Balducci et al., 2010; Lauren et al., 2009). This interaction has been shown to mediate the toxic effects of Aβ on LTP and synaptic function in vitro (Lauren et al., 2009), and on certain tests of memory in vivo (Gimbel et al., 2010). However, conflicting reports exist, where the effects of Aβ have been found to be independent of PrP (Balducci et al., 2010; Calella et al., 2010; Kessels et al., 2010). If PrP does mediate Aβ toxicity, it becomes an attractive new target for therapy in AD. The reasons for the contradictory findings are unclear, but in each case, despite some methodological differences, the role of PrP has been assessed by comparing Aβ toxicity in wild-type and embryonic PrP-null (PrP^{0/0}) mice. The aim of this study was to examine the role of PrP in mediating Aβ effects using two experimental paradigms. First, in PrP^{0/0} mice as above, and second, using RNAi for acute knockdown of PrP, to model the effects of a PrP-targeted treatment.

We measured dendritic spine loss induced by injection of synthetic Aβ oligomers (1 μM) into the hippocampus, as this is associated with both memory deficits and loss of LTP. In wild-type (WT) and PrP^{0/0} mice, we found that Aβ-mediated spine loss was independent of PrP in hippocampal slices, and also in vivo, after injection of Aβ. Spine density was equally reduced by Aβ treatment in WT (n = 70 dendrites from 3 separate mice ± SEM) and PrP^{0/0} (n = 70 dendrites from 3 separate mice ± SEM) mice, in each system (Fig. 1). However, when PrP was acutely depleted in adult WT mice using lentivirally-mediated RNAi in the hippocampus, we found significantly less spine loss post Aβ treatment (n = 150 dendrites from 6 separate mice ± SEM) than in animals given control virus and Aβ (n = 100 dendrites from 4 separate mice ± SEM) (Fig. 1).