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Proteomics reveals that a high-fat diet induces rapid changes in hypothalamic proteins related to neuronal damage and inflammation

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A diet high in long chain saturated fat is a key cause of obesity via the induction of insensitivity to the anorexigenic effect of both leptin and insulin in the hypothalamus. This effect has been linked to inflammation in the hypothalamus but only after several weeks on the diet[(1)]. We have shown that high-fat diet-induced insulin insensitivity is seen within 3 days in mice. To further investigate the mechanisms underlying this induction we fed 12 week old male C57Bl/6J mice a low- or high-fat diet: 10% or 60% (Kcal) from fat (D12450B and D12492 respectively, Research Diets, USA) for 3 days. Insulin sensitivity was assessed by intraperitioneal glucose tolerance tests (IPGTT) and proteomics was used to determine changes in hypothalamic proteins. Body composition was measured using MRI, liver lipid content measured by oil red O staining. Mice on the high-fat diet showed increased adiposity, liver lipid content and insulin insensitivity with a 48% increase in area under the curve (AUC) compared to control animals. Hypothalamic protein samples analysed by 2D eletrophoresis revealed profound changes after 3 days on the high-fat diet, which when identified by LC/MS/MS were found to be proteins associated with neuronal damage particularly inflammation, ischemia and apoptosis including collapsin response mediated protein 2 (CRMP-2), cyclophilin A, alpha-enolase and apolipoprotein E[(2–5)]. Thus, there appears to be a rapid, within days, effect of high-fat diet on the hypothalamus which is indicative of neuronal damage.

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