Fatty acid metabolism in the hypothalamic parenchyma of mice is limited by transport across the blood brain barrier

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Obesity is associated with lipid accumulation in non-adipose tissues, which can result in “lipotoxic” outcomes such as impaired insulin action and apoptosis. We have recently shown that “lipotoxicity” extends to the central nervous system (CNS), such that obesity induced by high-fat feeding results in lipid deposition in the hypothalamus of mice. Lipid deposition in the brain is postulated to affect energy homeostasis and peripheral insulin action. Recent studies have challenged the dogma that the CNS does not oxidise fatty acids. Interestingly, diets that contain medium-chain fatty acids (MCFA) have been shown to induce fatty acid oxidation, increase energy expenditure and improve insulin action when compared with diets containing long-chain fatty acids (LCFA). Hence, the aim of this research was to compare the metabolic fates of MCFA and LCFA in the hypothalamus.

Free fatty acid (FFA) metabolism was assessed using radiometric methods in immortalised and primary murine neurons, isolated hypothalamic sections *ex vivo* and in mice *in vivo*. Immortalised hypothalamic-derived neurons and primary neurons are capable of transporting fatty acids across the plasma membrane, oxidizing fatty acids and storing fatty acids as triglycerides. The oxidation to storage ratio was 1:5 for LCFA and 4:1 for MCFA. Further studies showed that whole hypothalamus isolated from lean mice exhibit a preference for fatty acid oxidation rather than storage (3:1 ratio). LCFA and MCFA administered directly into the cerebrospinal fluid via the lateral ventricle in conscious mice were both oxidised and stored as glycerides (1:4 and 25:1 oxidation to storage ratio, respectively). When LCFA were administered via the carotid artery, CNS fatty acid uptake and storage were negligible. Conversely, MCFA were readily able to cross from the circulation to the CNS and were oxidised and stored at a 20:1 ratio.

Thus, the parenchyma of the hypothalamus (including neurons) is capable of fatty acid transport, oxidation and storage. However, LCFA uptake is negligible when fatty acids are delivered by their normal route, suggesting that MCFA have a greater influence on CNS fatty acid metabolism *in vivo*.