High fat diet influences brain cholesterol metabolism in wildtype and apolipoprotein E-knockout mice

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Both *in vivo* and *in vitro* studies show an interaction between cholesterol and amyloid-deposition, a hallmark of Alzheimer's disease (AD). Alterations in cerebral cholesterol metabolism may affect the development and progression of AD. The main cholesterol transporter in the circulation and in the brain is apolipoprotein E (apoE). ApoE4, a human ApoE-isoform, is the major known genetic risk factor for AD. Previously, we reported that apoE is necessary for the maintenance of blood-brain barrier integrity during aging and protects against high fat diet induced neuropathology.
We investigated the effect of a high fat diet on brain cholesterol metabolism in presence or absence of apoE. Using gas chromatography-mass spectrometry, we measured levels of cholesterol, cholesterol precursors (lathosterol, lanosterol, desmosterol), cholesterol metabolites (24S-OH-cholesterol, cholestanol) and of plant sterols (campesterol, sitosterol) in brain and serum of wildtype (mE+/-) and apoE-knockout mice (mEko), on a high fat diet versus chow diet. As expected, in mEko mice, serum cholesterol levels increased dramatically (1212±233 mg/dl) compared to mE+/- mice (100±29 mg/dl), as a result of high fat diet. Yet, brain cholesterol levels were similar in all groups. Surprisingly, in both wildtype and apoE-knockout mice, a high fat diet decreases brain cholesterol precursor levels (high fat diet:78±18 versus chow diet:127±28 ng lathosterol/mg brain; p=0,001) and increases 24S-OH-cholesterol levels (High fat diet: 209±19 versus chow diet: 131±9 ng/mg brain; p= 0,000). In conclusion, cholesterol metabolism in the brain can be modulated by consumption of a high fat diet. This appears to be independent from serum cholesterol levels, presence of ApoE or BBB-integrity. Therefore, dietary intervention may be therapeutic targets for the treatment of AD.
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