HIGH FAT DIET DECREASES PLASMA ABETA LEVELS IN MICE OVEREXPRESSING HUMAN APP

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BACKGROUND

Sporadic Alzheimer's disease (AD) is influenced by a set of non-genetic risk factors, whereas dyslipidemia seems to play a crucial role. Interestingly, it was shown in mice overexpressing human ApoB-100, that a shift in the plasma lipoprotein composition towards higher LDL-cholesterol levels without dietary intervention is able to induce cognitive decline. To see whether this phenotype could be more pronounced by additional cholesterol uptake, a high-fat feeding study was conducted with animals overexpressing human ApoB-100 and/or human APP_{SL}.

MATERIALS AND METHODS

Animals of every genotype, $ApoBxAPP_{SL}$, ApoB-100, APP_{SL} and wild type (WT), received either a standard chow (normal diet, ND) or high-fat-diet (HFD) for 3 months. At an age of 6 months, all animals underwent several behavioral tests, including the Morris water maze (MWM) task. Abeta levels were assessed in brain and plasma samples with Meso Scale Discovery (MSD) based immunosorbent assay. Blood plasma was also analyzed for total cholesterol, HDL-cholesterol and LDL-cholesterol.

RESULTS

HFD feeding leads to the expected changes of the plasma lipid profile resulting in more atherogenic conditions in all genotypes, with the strongest response in ApoB-100 mice (Fig. 1).

Behavioral data show that HFD has no measureable impact on spatial learning in the MWM task compared to normal diet fed animals (Fig. 2). Swim speed and swim length did also not differ between genotypes and diets (data not shown).

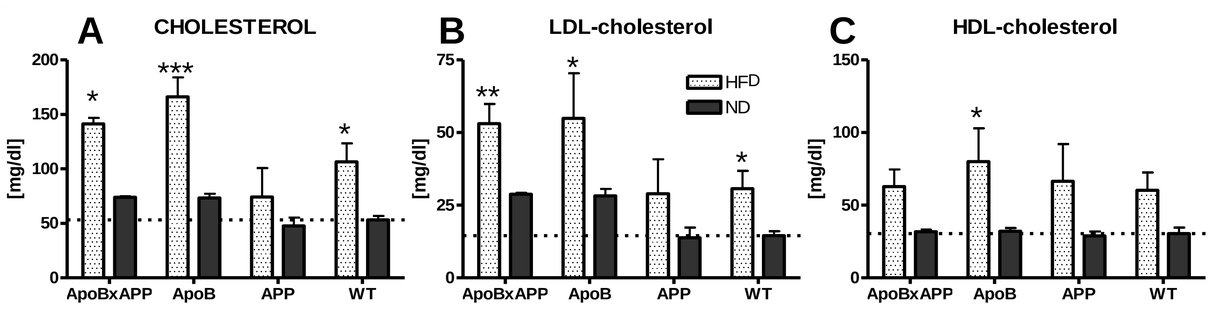

Figure 1. Effects of HFD on plasma lipids. Results of plasma lipid measurements evaluating (A) total cholesterol, (B) LDL-cholesterol and (C) HDL-cholesterol levels of HFD (n=5 per genotype) and ND (n=6-7 per genotype) fed animals. Statistical analysis: Two-way-ANOVA with Bonferroni post-test. *p<0.05, **p<0.01, ***p<0.001.

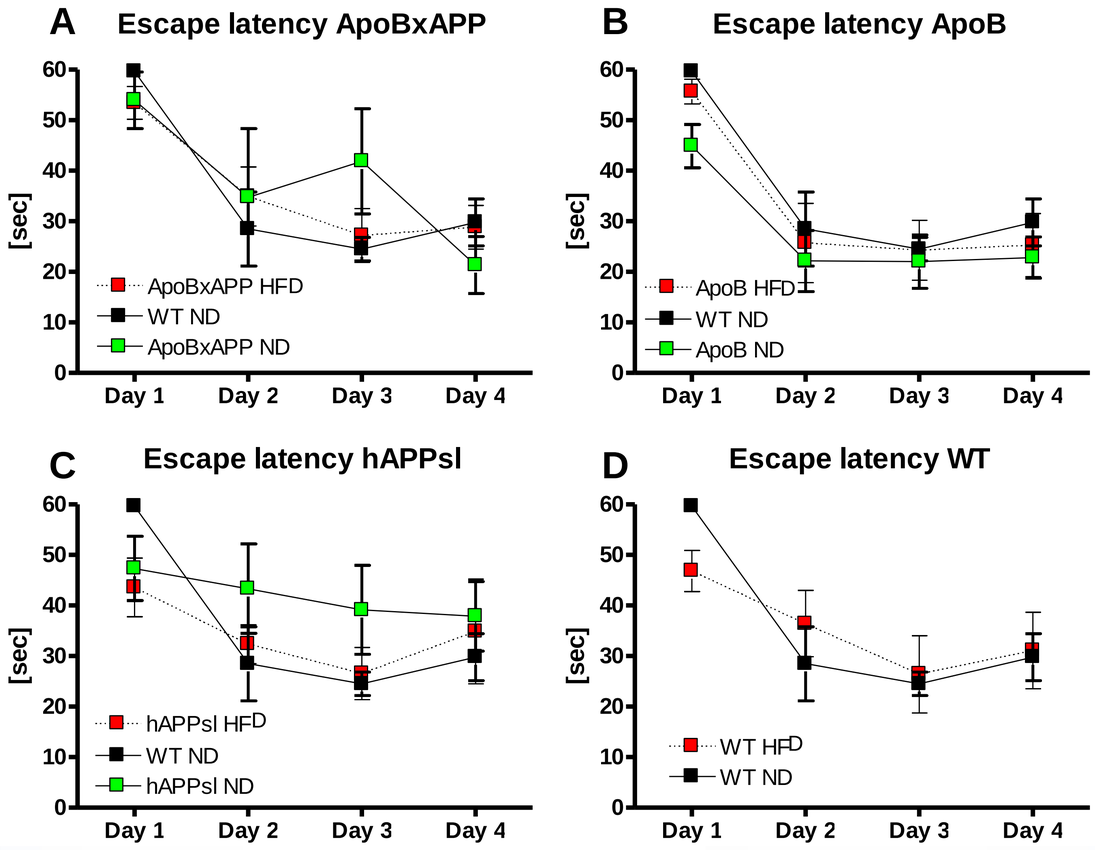

Figure 2. Spatial learning in HFD and ND fed animals. MWM learning curves showing escape latencies during 4 testing days of $ApoBxAPP_{SL}$ mice on HFD and ND versus WT on ND (A), ApoB mice on HFD and ND versus WT on ND (B), APP_{SL} mice on HFD and ND versus WT on ND (C) and WT mice on HFD and ND (D). Number of animals: 5-7 per group. Statistical analyses: Two-way-ANOVA with Bonferroni post-test.

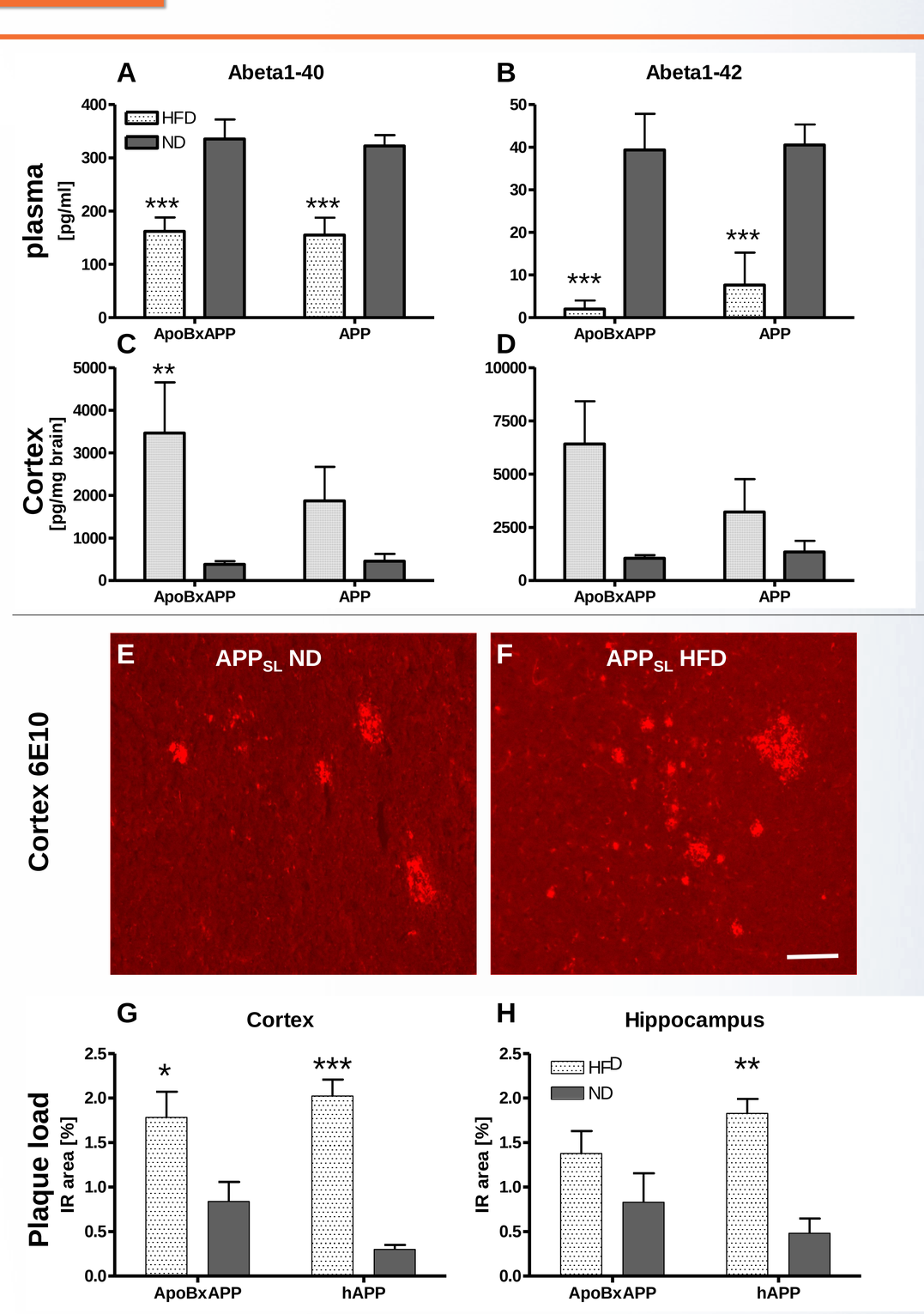

Figure 3. Influence of HFD on plasma and cortical Abeta levels and plaque formation. Plasma levels of (A) Abeta1-40 as well as (B) Abeta1-42 significantly decreased on HFD compared to ND in both human APP overexpressing strains, $ApoBxAPP_{SL}$ and APP_{SL}. In contrast, cortical levels of (C) Abeta 1-40 and (D) Abeta1-42 in formic acid containing fractions showed a tendency to be increased on HFD. Number of animals: 5-6/group. Representative pictures of increased 6E10 staining on brain slices of APP_{SL} mice on HFD (F) compared to APP_{SL} mice on ND (E). Scale bar 100µm. Quantitative immunohistochemical detection of cortical (G) and hippocampal (H) plaque load on 10-µm-thick mounted sections derived from 5 different mediolateral levels per animal incubated with 6E10 antibody. Number of animals: 4-6 animals/group. Statistical analyses: Two-way-ANOVA with Bonferroni post-test. *p<0.05, **p<0.01, ***p<0.001.

Interestingly, HFD leads to a significant decrease of Abeta1-40 and Abeta 1-42 levels in the plasma of $ApoBxAPP_{SL}$ and APP_{SL} mice (Fig. 3 A & B).

Together with the increase of insoluble Abeta species in the brain of HFD-fed animals (Fig. 3 C & D), impaired clearance of Abeta from the brain due to HFD feeding can be assumed. Since overexpression of human APP is restricted to neuronal tissue, almost all of the human Abeta in the plasma must be brain-derived. Therefore, a reduction of human Abeta in the plasma of transgenic animals is in line with this theory of 'impaired clearance' caused by HFD.

Histological investigations of plaque load in $ApoBxAPP_{SL}$ and $hAPP_{SL}$ mice showed a significant increase of cortical plaque load in both human APP overexpressing strains, $ApoBxAPP_{SL}$ and APP_{SL} (Fig. 3 G). In the hippocampus only plaque load changes in APP_{SL} mice reached significance (Fig. 3 H).

CONCLUSIONS

While HFD barely influenced behavioral aspects, it strongly affected cerebral Abeta clearance and plaque load in both strains of human APP overexpressing mice, $ApoBxAPP_{SL}$ and APP_{SL}.

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