

The ADAM10-NEGR1 axis in hypothalamus and hippocampus is modulated by high-fat-diet and germ-free status

P-1240

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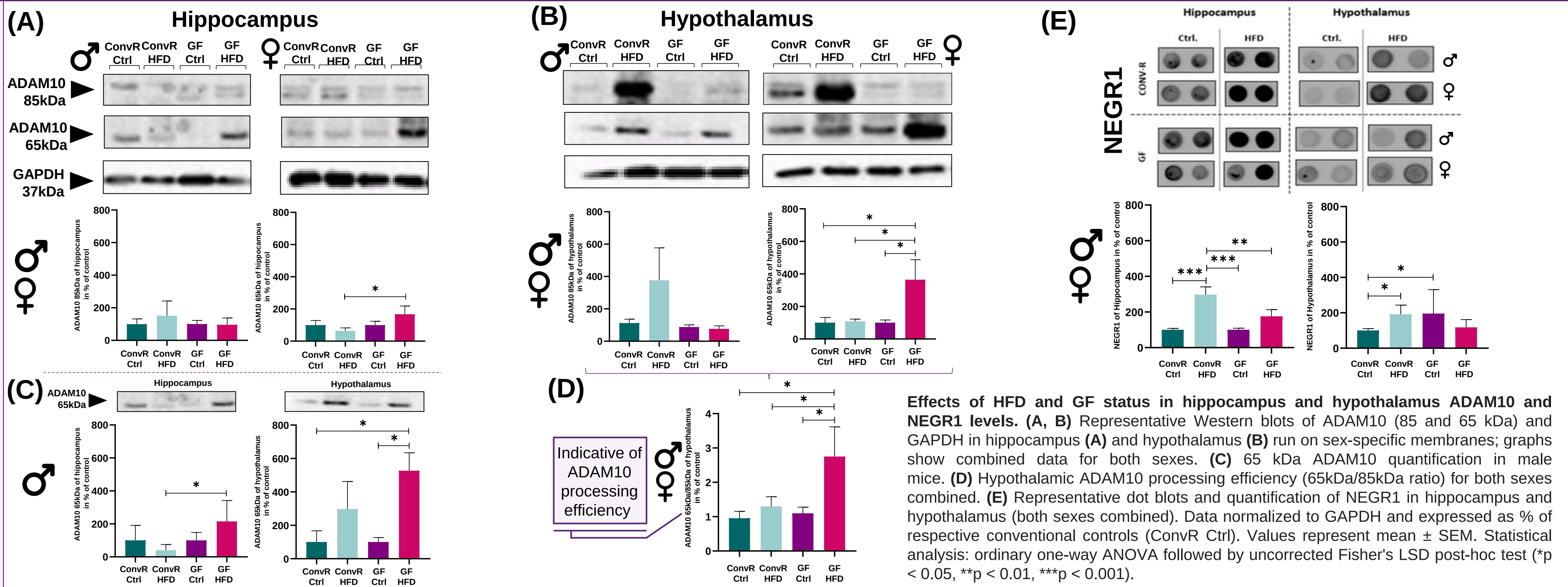
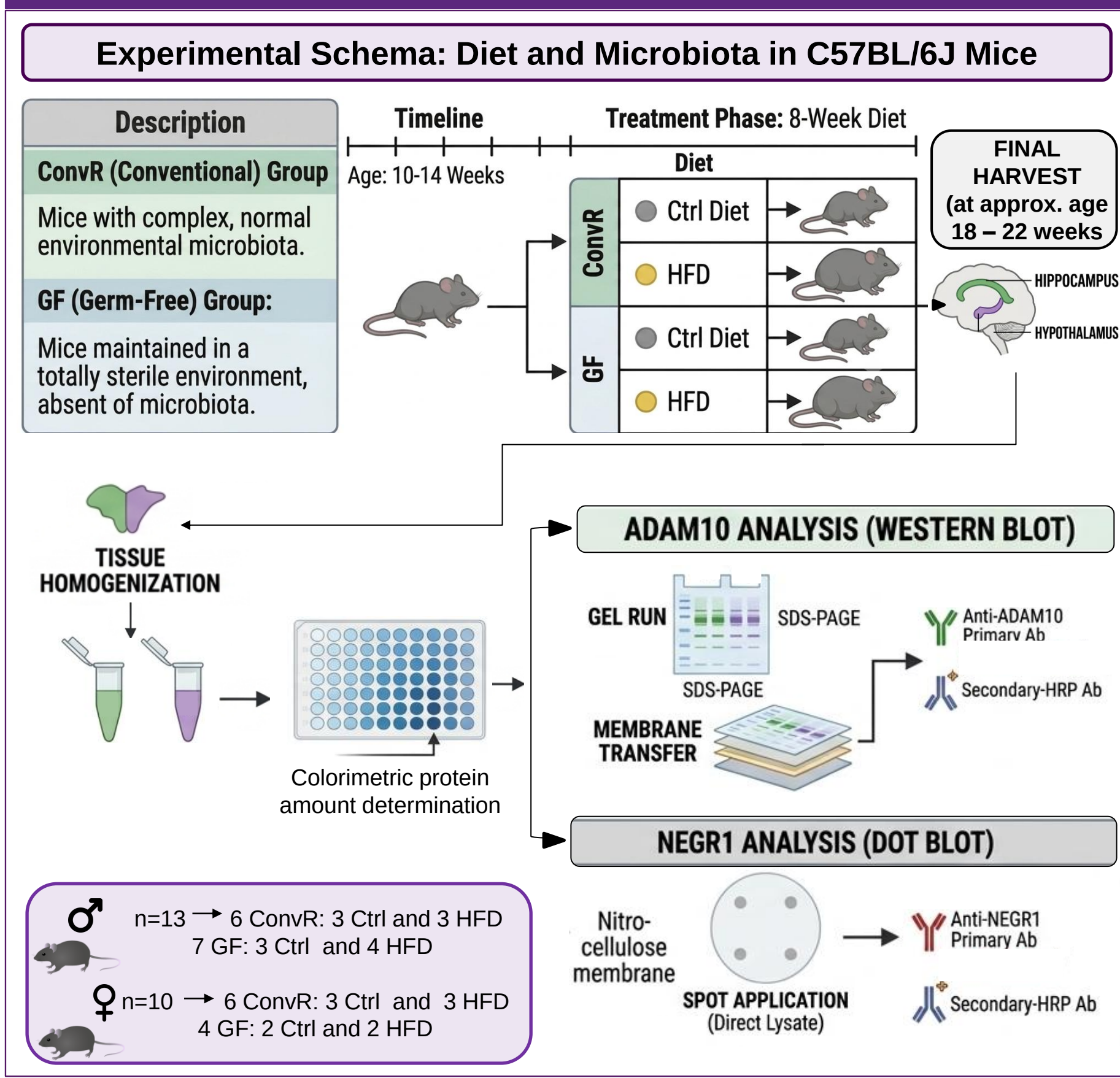
Germ-free status plays a key role in gating diet-induced ADAM10 activation and NEGR1 alterations in the hypothalamus and hippocampus.

INTRODUCTION

RESULTS

Type 2 diabetes mellitus (T2DM), driven by chronic hypercaloric intake, is a major risk factor for the development of Alzheimer's disease (AD) (1). High-fat diets induce systemic insulin resistance and peripheral inflammation, which can impair homeostatic and cognitive centers, specifically the hypothalamus and the hippocampus (2). The neuroprotective α -secretase ADAM10 modulates these regions by cleaving Neuronal Growth Regulator 1 (Negr1), an immunoglobulin-like cell adhesion molecule associated with energy balance and synaptic plasticity. This proteolytic cleavage releases a soluble form of Negr1 that binds to Fibroblast Growth Factor Receptor 2 (FGFR2) to promote neuronal health (3). Interestingly, germ-free (GF) mice exhibit a protected metabolic phenotype, remaining resistant to diet-induced obesity and metabolic dysfunction (4). This study aimed to determine whether a high-fat diet alters the expression of ADAM10 and Negr1 in the hypothalamus and hippocampus, and whether the absence of gut microbiota in GF mice prevents potential diet-induced alterations in these proteins compared to conventionally raised (ConvR) mice.

METHODS



In the hippocampus (A), combined analysis of both sexes showed that GF HFD increased ADAM10 65 kDa levels vs. ConvR HFD. Independent analysis of male mice (C) demonstrated a significant modulation of this 65 kDa isoform, with distinct protein variations between groups visible uniquely in male Western blot membranes (ConvR HFD vs GF HDF; ConvR and GF Ctrl vs GF HFD). In the hypothalamus (B), ADAM10 85 kDa levels remained unaltered across all groups, whereas ADAM10 65 kDa was significantly upregulated in the GF HFD cohort. In the hypothalamic ADAM10 65kDa/85kDa ratio (D) (both sexes combined) was significantly elevated in the GF HFD group. Regarding NEGR1 levels (E), tissue-specific profiles were observed: in the hippocampus, HFD induced a significant upregulation in conventional mice that was blunted by the germ-free status (GF HFD vs. ConvR HFD); in the hypothalamus, conventional mice showed HFD-induced elevation, while germ-free mice exhibited higher baseline NEGR1 levels under a standard control diet (GF Ctrl vs. ConvR Ctrl).

CONCLUSION

Diet-induced molecular shifts in the brain are modulated by the gut microbiota, presenting distinct regional profiles. In the hypothalamus, GF HFD mice display a significant upregulation of ADAM10 65 kDa and an increased 65kDa/85kDa processing ratio in the combined-sex analysis, alongside distinct, sex-dependent profiles, particularly in male mice. In contrast, germ-free status completely blunts the HFD-induced upregulation of NEGR1 in the hippocampus. These findings demonstrate tissue- and possible sex-specific differences in the regulation of the ADAM10 and NEGR1 pathways under dietary stress and altered microbiota states.

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CONTACT

ACKNOWLEDGEMENTS

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ACKNOWLEDGEMENTS

The first author was supported by CNPq (201150/2024-7)

CNPq

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