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Investigating plasma and brain cholesterol esterification in patients with amyotrophic lateral sclerosis

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Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease, with metabolic alterations, abnormal cholesterol and lipid levels in the bloodstream and central nervous system (CNS). Similar to plasma, cholesterol in the cerebrospinal fluid (CSF) is carried by lipoproteins known as "HDL-like particles," due to their close similarity in density and composition to plasma HDL. Lecithin cholesterol acyltransferase (LCAT) is a key enzyme in HDL metabolism, catalysing cholesterol esterification in both plasma and CSF, thus facilitating HDL maturation. This study aimed to investigate cholesterol esterification in plasma and CSF and to characterize HDL subclass distribution in patients with ALS. The study included 20 ALS patients and 20 controls, in whom lipoprotein profile and cholesterol esterification were evaluated in both plasma and CSF. Plasma lipid levels were similar between patients and controls; however, the amount of discoidal preβ-HDL was significantly reduced in ALS patients compared to controls (8.5±4.9% vs 13.6±4.1%, $p<0.0001$). A significant increase in CSF unesterified cholesterol levels was observed in ALS patients compared to controls (0.22±0.07 mg/dL vs 0.15±0.04 mg/dL, $p<0.01$), leading to an increased unesterified/total cholesterol ratio in ALS patients (0.52±0.12 vs 0.40±0.12, respectively). While plasma cholesterol esterification remained unchanged in ALS patients, the cholesterol esterification rate was significantly reduced in their CSF (0.12±0.08 vs 2.41±1.98, $p<0.01$), consistent with the previous data. In conclusion, these results suggest a hampered cholesterol esterification in the CSF of ALS patients. Whether this defect is related to the severity or progression of the disease remains to be defined.

Neutrophil behavior during the metabolic adaptations to short term high fat feeding

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Background and Aims: Neutrophils participate to the chronic metabolic consequences of High Fat Diet (HFD). Nevertheless, neutrophils are characterized by short half-life which is determined by a fine tuning in expression and function of CXCR4, which dictates the egress from the bone marrow (BM), and CXCR2, which facilitates their mobilization from BM and the patrolling activity in the periphery. In the quest to study the behavior of the neutrophil with the short-term consequences of HFD feeding, we studied whether the metabolic adaptations affect blood neutrophil count and the membrane expression of their indirect markers of function.
Methods: To assess the gluco-metabolic impact of a short-term HFD feeding, indirect calorimetry and plasma glucose dosage were performed on mice previously fed a HFD (60% Kcal from fat) for seven days, followed by immunophenotyping of blood over 24 hours. To test whether changes in circulating neutrophil count during short-term HFD feeding were related to a differential egress from the BM, we repeated the same experimental design in mice harboring a conditional deletion of CXCR4 (CXCR4fl/flMrp8Cre+).
Results: Short-term HFD feeding was sufficient to induce a profound metabolic impact (e.g. reduced respiratory exchange ratio, increased energy expenditure, and insulin levels), and to induce an increase of circulating neutrophils (p=0,052), without impacting other leukocytic fractions over 24 hours, compared to chow diet feeding mice (20% Kcal from fat). HFD feeding significantly altered the expression pattern of multiple membrane markers of neutrophil function (CD11b, CD62L, CXCR2) over 24 hours, driving neutrophils toward a phenotype featuring increased migration and activation. Finally, the CXCR4fl/flMrp-8Cre+ mice, which present significantly higher circulating neutrophilia, showed lower insulin sensitivity upon HFD compared to WT.
Conclusions: We suggest that the metabolic adaptations induced by a short-term exposure to HFD affect neutrophil behavior, surmising it as an appealing target for cardio-metabolic diseases.