

Neonatal modulation of gut digestion and microbiota by addition of dairy lipids and probiotic *L. fermentum* CECT 5716 in infant formula programs adult gut microbiota and physiology in a minipig model

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Postnatal nutrition has long-lasting impacts on adult metabolism and gut physiology. Gut microbiota has been identified as a key actor of this nutritional imprinting. We hypothesized that improving infant formulas (IF) to mimic the composition of human milk could provide short- and long-term health benefits. We therefore investigated the short- and long-term effects of addition of dairy lipids (DL) and probiotic *Lactobacillus fermentum* CECT 5716 (Lf) in IF on gut microbiota and physiology in a Yucatan minipig model.

Forty-eight piglets received a formula containing only plant lipids (PL), a half-half mixture of PL and DL (DL), or a half-half mixture of PL and DL supplemented with Lf (DL±Lf) from postnatal day (PND) 2 to 28. Twenty-two piglets were euthanized at PND28 whereas twenty-six pigs were weaned on a standard diet for 1 month, then challenged with a hyperenergetic diet for 3 months and euthanized at PND140. At PND28, DL±Lf piglets displayed higher gastric protein hydrolysis and higher proximal jejunal and ileal diglycerides and cholesterol contents compared to PL. In addition to changes in intestinal permeability and density of goblet cells, faecal metabolome and microbiota composition were modified by the IF composition. At family level, operational taxonomic units (OTUs) belonging to *Ruminococcaceae* and *Prevotellaceae* were higher in DL±Lf compared to PL whereas those of *Bacteroidales* S24-7 group were lower compared to PL.

At PND140, OTUs belonging to *Ruminococcaceae* and *Prevotellaceae* families were increased in DL compared to PL while OTUs belonging to *Lachnospiraceae* family were increased in DL±Lf compared to PL. Ileal trans- and paracellular permeabilities were higher in DL±Lf compared to PL, while jejunal LPS passage and ileal explant LPS-induced pro-inflammatory cytokine (TNF α and IL-8) secretions were decreased.

This study demonstrates IF composition-induced changes in neonate gut physiology with a long-term programming effect involving gut microbiota.