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Alterations in ileal and colonic permeability by chronic intake of high-lipid diets enriched with omega 3, omega 6 or saturated fat

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Gut permeability is a key function often incriminated in the development of local and systemic inflammation. Chronic consumption of high-fat diets leads to obesity and inflammation. Data in mice revealed a causal increase in intestinal permeability to bacterial lipopolysaccharide (LPS) that may be responsible for adipose tissue development and inflammation[1]. Whether intestinal or colonic barrier can be modulated by omega-6 (O6) or omega-3 (O3) PUFA in the context of high-fat diet-induced obesity is poorly understood. Intestinal epithelial barrier *in vitro* is strengthened by both O6 (e.g. DGLA, AA) and O3 (e.g. EPA, DHA) fatty acids[2]. *In vivo*, rats chronically fed high fat diets enriched in PUFA did not show different paracellular permeabilities in the jejunum, compared to rats fed a diet rich in saturated fat[3]. Whether colonic permeability is altered has not been reported. We hypothesized that PUFA-enriched diets modulate gut permeability differentially according to permeability (para- and trans-cellular) pathway and gut site.

This hypothesis was tested in 16 obese adult minipigs fed for 2 months with iso-protein and iso-calorie high-fat (12 %) diets based on lard (saturated fat, S), sunflower oil (rich in O6), or fish oil (rich in O3) ($n = 5$, 6 and 5, respectively). At the end of the trial, ileal and colonic mucosa were collected and both para- and trans-cellular permeability were investigated with fluorescein isothiocyanate-dextran 4 (FD4, MW 4 kDa) and horseradish peroxidase (HRP, MW 40 kDa) in Ussing chambers[4]. Gut permeability was assessed without (basal) and with an inflammatory challenge (*E. coli* LPS added at 0.1 and 10 μg/ml in Ussing chambers). Data were analysed by SAS using a MIXED model for testing the effects of diet, LPS challenge and interaction at each site. The experiment was approved by the local Ethical Committee.

After two months of regimen, body weight was not different between diet groups. Ileal mucosa density (g/cm length) was not affected by the diet (not measured for colon). Ileal permeability to FD4 was not influenced by the diet in the basal state but it tended to be higher with O3 compared to O6 diet after LPS challenge (e.g. with LPS 0.1 μg/ml: 1272 (389), 775 (355) and 1723 (389) ng/cm^2/h; $P = 0.095$). Interestingly, basal colonic permeability to FD4 was higher with O3 compared to O6 diet (692 (sem, 165), 509 (150) and 1032 (165) ng/cm^2/h for diets based on saturated, O6 and O3 FA, respectively; $P<0.05$). Dietary treatments did not affect basal ileal or colonic permeability to HRP. However, both ileal and colonic permeability to HRP tended to be higher with O3 than O6 diet after LPS challenge (e.g. ileal HRP flux with LPS 0.1 μg/ml: 199 (142), 106 (130) and 492 (142); $P = 0.067$).

Collectively, our data indicate that gut permeability is modulated by dietary FA source in the context of obesity, regionally and according to permeability pathway. Para-cellular permeability in the colon (but not in the ileum) was affected in the basal state by diet FA composition. Surprisingly, it was higher with the O3 as compared to O6-enriched diet (diet based on saturated fat being intermediate). The same trends for differences between O3 and O6 diets on para- or trans-cellular permeability were also revealed under inflammatory condition (LPS). Interestingly, our data are consistent with the observations that blood-brain barrier was also higher, and the activation of brain areas (e.g. prefrontal cortex and basal nuclei) involved in food intake regulation was lower, with the O3 than the O6 diet[5].

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