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Metabolic impact of dietary lipids: towards a role of unabsorbed lipid residues? ☆

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Abstract – The metabolic impact of dietary lipids needs to be considered beyond the fatty acid profile and energetic value of such lipids. Fatty acids are the building blocks of the different lipid molecules, including triacylglycerols and phospholipids, which are organized within various supramolecular structures such as emulsion droplets. These structures can also be naturally present or incorporated *a posteriori* in different food matrices. Gut health including its barrier function and microbiota is now recognized as a major player in cardiometabolic health. Even if more than 95% of dietary lipids are absorbed by the intestine to reach the bloodstream within the chylomicrons, a small proportion that is not absorbed is however able to interact with the microbiota and the cells of the distal intestine. The present non-exhaustive review will summarize briefly recent work on the impact of dietary lipids on absorption and their metabolic fate in the intestine, in particular on endotoxemia and low-grade inflammation related to obesity. Functional lipids are important ingredients used in food formulation and recent work has revealed the potential impact of some food emulsifiers on metabolism and inflammation in rodents in line with intestinal effects. Of particular interest in this review will be also recent findings on the benefits of dairy polar lipids on human lipid metabolism and their beneficial effects on metabolic inflammation in preclinical models. The review will also address the underlying mechanisms related to the metabolic fate of specific lipids such as sphingomyelin in the distal intestine, the microbiota and some actors of the intestinal barrier. Finally, these recent findings will be considered in the concept of the “food matrix effect” opening perspectives in the nutritional management of metabolic disorders.

Keywords: nutrition / fat / oil / emulsifier / endotoxin / inflammation / polar lipids / intestine / gut barrier

Résumé – Impact métabolique des lipides alimentaires : rôle des résidus lipidiques non absorbés ?

L'impact métabolique des lipides alimentaires doit aujourd'hui être considéré au-delà de leur profil en acides gras et de leur apport énergétique. Les acides gras sont les briques élémentaires de différentes molécules lipidiques, dont les triglycérides et les phospholipides, qui sont organisées en différentes structures supramoléculaires telles que les gouttelettes d'émulsion. Ces structures peuvent être présentes naturellement ou incorporées *a posteriori* dans différentes matrices alimentaires. En parallèle, une bonne santé intestinale, incluant sa fonction barrière et son microbiote, est désormais reconnue comme un acteur majeur de la santé cardiométabolique. Même si 95 % des lipides alimentaires sont absorbés par l'intestin pour rejoindre la circulation sanguine au sein des chylomicrons, une faible proportion restante et non absorbée est néanmoins capable d'interagir avec le microbiote et les cellules de la partie distale de l'intestin. Cette revue non-exhaustive résumera certains travaux récents portant sur l'impact des lipides alimentaires sur leur absorption et leur devenir métabolique dans l'intestin, mais aussi sur l'endotoxémie et l'inflammation à bas bruit liée à l'obésité. Les lipides fonctionnels sont des ingrédients importants utilisés en formulation alimentaire et les impacts potentiels de certains agents émulsifiants sur le métabolisme et l'inflammation, en lien avec leurs effets dans l'intestin, ont récemment été mis en évidence chez les rongeurs. Cette revue s'intéressera aussi particulièrement aux découvertes récentes sur les bénéfices des lipides polaires laitiers sur le métabolisme lipidique chez l'Homme et sur l'inflammation métabolique dans les modèles précliniques. La revue abordera également les mécanismes

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sous-jacents en lien avec le devenir métabolique de lipides spécifiques comme la sphingomyéline dans l'intestin distal, ainsi que ceux en lien avec le microbiote et la barrière intestinale. Enfin, l'ensemble de ces nouveaux résultats sera mis en perspective dans le cadre du concept récent de l'« effet matrice alimentaire » qui ouvre des perspectives dans la prise en charge nutritionnelle des désordres métaboliques.

Mots clés : nutrition / matières grasses / huiles / émulsifiants / endotoxine / inflammation / lipides polaires / intestin / barrière intestinale

1 Introduction

Dietary lipids play a key role in metabolic health and the significance of intestinal fat metabolism to human health is increasingly recognized. Dietary lipids are ingested under different native forms or structures including triacylglycerols and phospholipids, which are organized within various supramolecular structures such as emulsion droplets. These structured lipids undergo the different steps of digestion and absorption all along the gastrointestinal tract, and inevitably interact with the local microbiota and its components but also with the intestine cells. Endotoxins, also called lipopolysaccharides (LPS), are a major component of the outer membrane of Gram-negative bacteria. The link between dietary lipids and endotoxins has emerged through the concept of metabolic endotoxemia developed during the last decade by [Cani *et al.* \(2007\)](#) and described in more details in previous reviews ([Laugerette *et al.*, 2011a](#); [Michalski *et al.*, 2016](#)) and within this special issue ([Caroff and Novikov, 2020](#); [Gérard, 2020](#); [Bellenger *et al.*, 2021](#)). Briefly, endotoxemia is defined by the presence of gut-derived LPS in the bloodstream, and the transient increase of endotoxin blood levels following ingestion of fat-rich meals is called “metabolic endotoxemia”. This concept is thus important to consider regarding the metabolic impact of dietary lipids involving mechanisms associated with the gut microbiota. Furthermore, the structured lipids contained in the diets provide saturated and unsaturated fatty acids that reach the small intestine after the digestion, but a small proportion of dietary lipids that are consumed can escape and reach the large intestine even in healthy individuals. The metabolic impact of such non-absorbed lipids and their metabolites remains poorly described while it could play a significant role. A potential role of lipid residues in the colon is all the more relevant given that in some diseases such as pancreatic diseases, cystic fibrosis, celiac and Crohn's diseases, the flow of undigested lipids to the intestine can be increased. Moreover, the increasing use of drugs such as Orlistat® to prevent absorption of fat from the small intestine also enhances the proportion of dietary fat reaching the colon.

In this context, the present non-exhaustive review will address the potential impact of lipid residues on lipid metabolism and inflammation related to metabolic diseases. The review will also show the relevance to consider the intestine notably the gut microbiota and the gut barrier when investigating the metabolic impact of dietary fats. Recent findings related to the metabolic impact of various lipid emulsifiers will be also highlighted.

2 Postprandial lipids, gut-derived LPS and gut permeability

During fat meal digestion, gut microbiota-derived endotoxins can cross the gut barrier to the bloodstream ([Erridge](#)

[et al., 2007; \[Ghoshal *et al.*, 2009\]\(#\)\) through a transcellular transport within intestinal cells associated with intestinal chylomicron secretion \(\[Ghoshal *et al.*, 2009\]\(#\); \[Laugerette *et al.*, 2011b\]\(#\)\) \(Fig. 1\). The relative enrichment of chylomicrons with LPS along the postprandial phase was reported higher in obese men compared to normal-weight individuals after ingestion of 40 g of fat \(\[Vors *et al.*, 2015\]\(#\)\). It should be noted that the postprandial accumulation of pro-inflammatory cytokine IL-6 was also correlated positively with the fasting plasma level of LPS-binding protein \(LBP\), a longer-term marker of endotoxin exposure that was higher in obese individuals \(\[Vors *et al.*, 2015\]\(#\)\). The uptake of LPS may occur in absorptive enterocytes thanks to the internalization of LPS. Indeed, LPS may be internalized by intestinal epithelial cells through TLR4 recognition and transported to the Golgi compartment \(\[Homef *et al.*, 2002\]\(#\)\), where newly assembled chylomicrons are located prior to their secretion. \[Ghoshal *et al.* \\(2009\\)\]\(#\) nicely explored in details this specific transcellular mechanism using both *in vitro* and *in vivo* studies, and demonstrated notably that LPS absorption was completely blocked by the addition of the inhibitor of chylomicron formation \(Pluronic L-81\), even though this inhibitor does not interfere with fat uptake into the enterocytes \(\[Ghoshal *et al.*, 2009\]\(#\)\). LPS in the gut lumen can also join the bloodstream thanks to paracellular transport due to gut permeability induced notably by high-fat diet. Such paracellular transport of LPS in the small intestine was demonstrated *ex vivo* in ileal explants of rats fed a Western diet \(\[Guerville *et al.*, 2017\]\(#\)\). This phenomenon was also recently observed in human small intestine using tests of permeability to macromolecules: jejunal explants of obese patients exposed to postprandial-like lipid micelles presented increased flux of 4 kDa-FITC dextran than jejunal explants of non-obese subjects, and this was enhanced in type 2 diabetic obese patients \(\[Genser *et al.*, 2018\]\(#\)\). Decreased gene expression of tricellulin in tight junctions also confirmed an alteration of the gut barrier integrity \(\[Genser *et al.*, 2018\]\(#\)\). Given that chylomicrons have high affinity for LPS \(\[Vreugdenhil *et al.*, 2003\]\(#\)\), it cannot be ruled out that chylomicrons can also transport LPS that have reached the lymph *via* the paracellular way.](#)

These studies reveal the importance of considering postprandial lipid absorption occurring in the upper intestine on inflammation-related mechanisms involving both the small intestinal microbiota and the gut barrier.

3 Lipid residues, intestinal microbiota and gut barrier integrity and function

3.1 Unabsorbed fatty acids: a sizeable fecal loss

Most studies about dietary fats and oils usually have focused on their absorption in the small intestine, where they may exert their metabolic effects after the free generated fatty

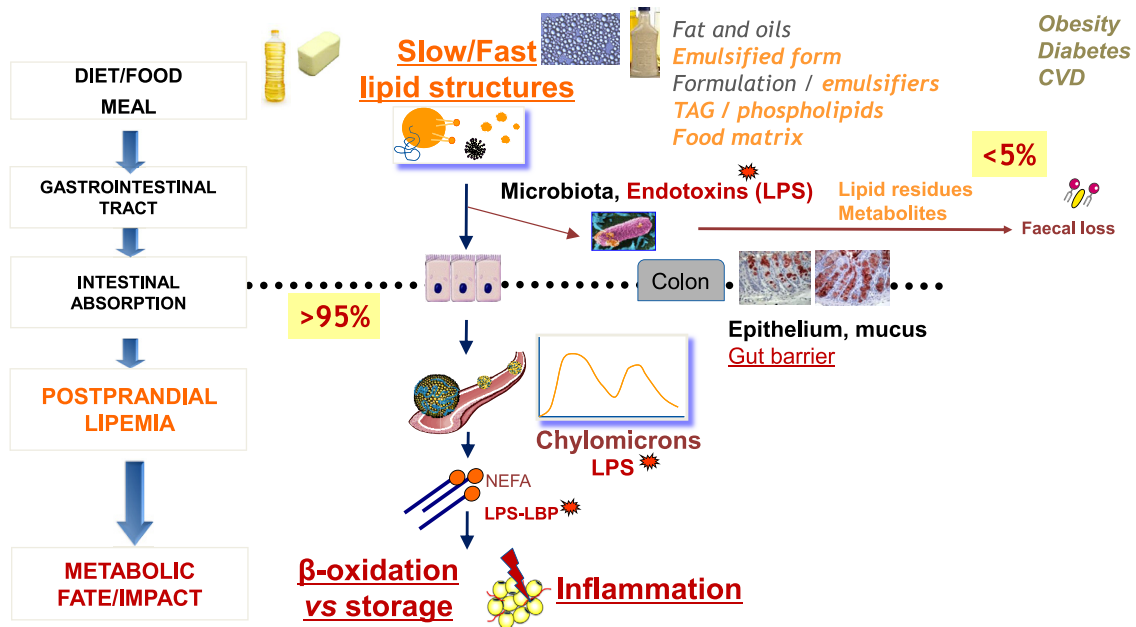


Fig. 1. Potential modulations of digestion, absorption and metabolic fate of the dietary lipids. Adapted from Michalski *et al.* (2013); Michalski *et al.* (2016, 2017); Bourlieu and Michalski (2015). LBP: lipopolysaccharide binding protein; LPS: lipopolysaccharides.

acids are re-esterified within chylomicrons and thereby enter the bloodstream. However, a small proportion of dietary fatty acids can remain unabsorbed in the gut lumen (on average <5%). A higher amount of saturated fatty acid soaps was found in the feces of rats fed cheese with higher vs lower content of palmitic and stearic acid (Ayala-Bribiesca *et al.*, 2018) and reviews summarize differences in intestinal lipid absorption according to the fatty acid composition and structure of different fats and oils (Berry and Sanders, 2005; Michalski *et al.*, 2013). Residual dietary fatty acids thereby reach the ileum and the colon where they can interact with the gut microbiota and intestinal cells (Fig. 1). Gabert *et al.* (2011) more precisely analyzed the fecal loss of stable isotope fatty acid tracers in the stools of 8 lean to obese subjects (BMI from 21 to 33.4 kg/m²) after the ingestion of a mixed meal containing ¹³C-labelled tripalmitin (C16:0) and ¹³C-triolein (C18:1 n-9). This study revealed that fecal loss of exogenous fatty acids occurred up to 72 h after meal ingestion, mainly in the form of non-esterified (“free”) fatty acids but also as TAG (Voortman *et al.*, 2002), meaning that some free fatty acids produced upon gastrointestinal lipolysis were not absorbed or were produced in the distal part of the intestine where they could not be absorbed (Fig. 2). Moreover, differential kinetics of fatty acid excretion were observed between subjects, either with a rapid peak between 12 h and 48 h after tracer ingestion or continuously decreasing from 24 h to 72 h (Fig. 2). Sizeable amounts of unabsorbed dietary fatty acids may thus transit through the colon for days after each meal. Significant differences in fecal excretion were observed according to the fatty acid: fecal excretion of ¹³C-palmitic acid was in the range of 5–10% of the ingested dose while that of ¹³C-oleic acid was in the range of 0.5–1% of ingested dose (Gabert *et al.*, 2011; Vors *et al.*, 2013) (Fig. 2).

3.2 Dietary PUFA and gut microbiota crosstalk – Production of potent lipid metabolites

Several studies have explored the effects of dietary fats and diets on the gut microbiota composition (for details, see Mekkala *et al.*, 2020 Gérard *et al.* OCL 2020 in the current issue). Briefly, the impact of saturated fatty acids has usually been evaluated through a fat overfeeding approach (high-fat diet), often resulting in (i) an increase in *Escherichia coli* and a decrease *Prevotella*, *Lactobacillus* sp. and *Bifidobacterium* sp. in the cecal content of mice (Cani *et al.*, 2008; Laugerette *et al.*, 2012), and (ii) an increase in Firmicutes and a reduction of Bacteroidetes, the two major bacterial phyla, in the feces of mice (Coelho *et al.*, 2019; Zhao *et al.*, 2019). Regarding long-chain omega-3 polyunsaturated fatty acids (PUFA) supplementation, it has been recently demonstrated that 4 g of EPA+DHA/day in healthy adults induced a decreased abundance of *Faecalibacterium* and an increased abundance of *Bifidobacterium*, *Roseburia*, and *Lactobacillus* (Watson *et al.*, 2018). In mice, linoleic acid-rich corn oil supplementation (C18:2 n-6) was reported to increase the abundance of *Enterobacteriaceae* and Proteobacteria (Ghosh *et al.*, 2013). Considering that a part of residual dietary fatty acids may reach the colon, their potential impact in reported effects of dietary fatty acids on the gut microbiota populations cannot be excluded. Indeed, gut bacteria can metabolize some unabsorbed dietary fatty acids leading to the production of fatty acid metabolites with their own metabolic effects. Recent studies also reported that some human probiotic bacteria such as *Lactobacillus rhamnosus* GG and *Bifidobacterium longum* NCC 2705 possess a low acyl hydrolase/lipase activity (Manasian *et al.*, 2020) and that some bacteria belonging to *Prevotella*, *Lactobacillus* and *Alistipes* genera are able to produce saturated long-chain fatty acids (Zhao *et al.*, 2018).

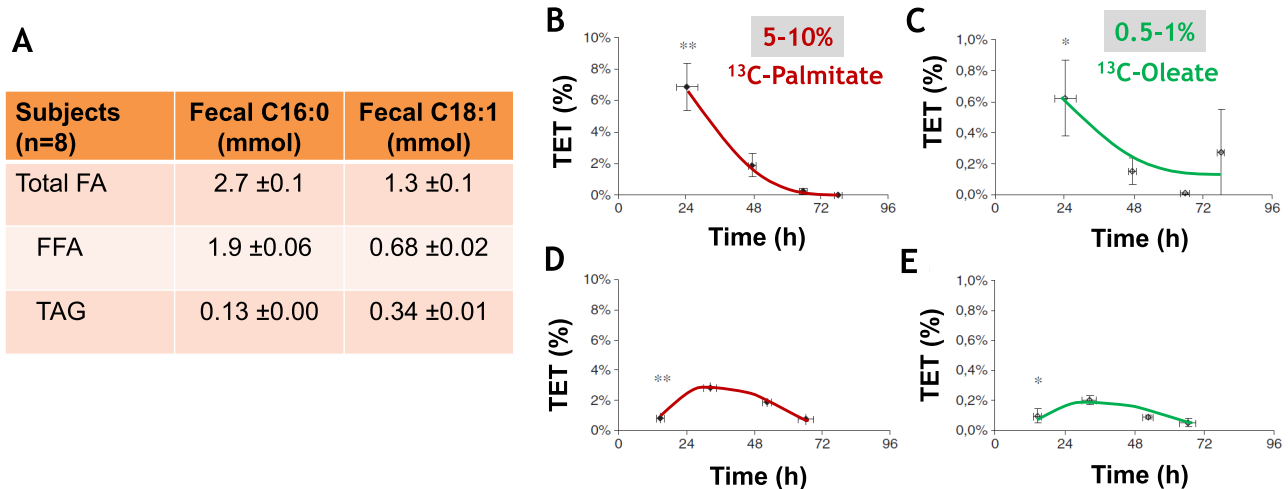


Fig. 2. Analysis of the fecal loss of stable isotope fatty acid tracers after ingestion of a fatty meal. (A) Cumulative amounts of fecal ^{13}C -labelled palmitic and oleic acids over 3 days after fatty meal ingestion. Excretion kinetics of ^{13}C -palmitic acid (B–D) and ^{13}C -oleic acid (C–E) for subjects with rapid excretion in stool #1 (B–C) and subjects with slower excretion in stools #2 and #3 (D–E). Adapted from Gabert *et al.* (2011). FA: fatty acids; FFA: free fatty acids; TAG: triacylglycerols; TET = total excretion tracer, expressed per day as a percentage of the ingested dose; TFA: total fatty acids.

These mechanisms potentially involved in the production of free fatty acids into the colon remains poorly studied.

Some bacterial species belonging to the *Lactobacillus* genus are able to metabolize dietary PUFA as a detoxifying mechanism in the gastrointestinal tract. *L. plantarum* (*Lactoplantibacillus plantarum* in the new taxonomy) generates hydroxyl fatty acids, oxo fatty acids and conjugated fatty acids (CLA) from linoleic acid (LA, n-6 PUFA) (Kishino *et al.*, 2013). Recent *in vitro* and *in vivo* studies demonstrated that PUFA-derived bacterial metabolites might exert anti-obesity and anti-inflammatory effects (Miyamoto *et al.*, 2015; Ohue-Kitano *et al.*, 2017). Miyamoto *et al.* (2019) demonstrated that HYA (10-hydroxy-*cis*-12-octadecenoic acid, also called 10-HOE) produced from LA (i) activated GPR40 and GPR120 receptors, inducing the secretion of the incretin hormone GLP-1 by intestinal L-cells, and (ii) suppressed lipid absorption through the increase of peristalsis in HFD-induced obese mice. Additional *in vitro* experiments demonstrated that HYA may exert anti-inflammatory effects inhibiting cytokine production in mice intestines and LPS-induced maturation of dendritic cells (Bergamo *et al.*, 2014), and inhibits $\text{TNF}\alpha$ - and DSS-induced adverse effects on the expression of tight-junction proteins (Miyamoto *et al.*, 2015). Interestingly, Gao *et al.* (2019) reported recently that HYA can be used as a substrate by some Bifidobacteria such as *Bifidobacterium breve* species to generate CLA. Regarding omega-3 PUFA, α -linolenic acid (ALA) can be metabolized by lactic acid bacteria into 13-hydroxy-9(Z),15(Z)-octadecadienoic acid (13-OH) and 13-oxo-9(Z),15(Z)-octadecadienoic acid (13-oxo) with anti-inflammatory effects. Indeed, such metabolites were reported to promote the polarization of M2-type macrophages and their accumulation in the lamina propria of the small intestine, involving the GPR40 receptor pathway (Ohue-Kitano *et al.*, 2017).

3.3 Fatty acid residues and gut barrier

The mucus layer is also a critical component of the gut barrier that can be modulated by dietary fat. Benoît *et al.*

(2015a) demonstrated that 5-day administration of palm oil to rat pups resulted in more colonic surface covered by mucus-secreting goblet cells, associated with more palmitic acid in colon content compared to those fed with rapeseed oil or sunflower oil, which did not differ from the control. This was associated with a higher transmucosal electrical resistance of the colon *ex-vivo*, revealing a better gut barrier integrity in rat pups after short-term palm oil administration (Benoît *et al.*, 2015a). More recently, Escoula *et al.* (2019) demonstrated that palmitic acid decreased the secretion of MUC2 (mucin) in LS174T goblet cells, which was restored by co-incubation with EPA or DHA (see also Bellenger *et al.* in this special issue). Therefore, the impact of palmitic acid on mucus cells may depend on the model and the physiological status. Interestingly, in several mouse studies investigating the impact of different high-fat diets on adiposity and metabolic inflammation (*e.g.* pasture cream vs standard cream; 45% milk fat vs 20% milk fat), we observed that the high-fat diet induced an increased number of colonic goblet cells, which was also related to lower metabolic alterations (Benoît *et al.*, 2014, 2015b). Therefore, the contribution of a potential effect of residual non-absorbed palmitic acid cannot be excluded in the reported differential impact of palmitic acid/palm oil on mucus layer.

3.4 Dietary fat and intestinal crosstalk between bile acids and gut microbiota

Bile acids have pleiotropic roles in lipid metabolism including significant functions in the digestion and absorption of fats. The normal range for serum total bile acids is 0–15 $\mu\text{mol/L}$ (Barnes *et al.*, 1975). However, the size of bile acid pool is increased and its composition altered in numerous hepatic diseases such as chronic hepatitis or cholestatic liver diseases and cardiometabolic diseases including type 2 diabetes. Bile acids are amphipathic molecules with both hydrophilic and highly hydrophobic faces that may exert

detergent effects. According to the degree of hydrophobicity, bile acids could either be highly toxic (hydrophobic ones) or exert anti-inflammatory effects (hydrophilic ones) (Chiang, 2013). Derived from the oxidation of hepatic cholesterol, primary bile acids are produced, conjugated and stored in the gallbladder. After meal ingestion, they are released into the intestinal lumen to form mixed micelles with phospholipids and lipolysis products (free fatty acids, monoglycerides (MAG)), thus facilitating lipid digestion by pancreatic enzymes (PLA2, BSSL, PLRP2) of substrates present in these micelles (phospholipid, MAG) as well as the micellar solubilization, dispersion and transport of lipolysis product towards the enterocytes (Carriere *et al.*, 1993; de Aguiar Vallim *et al.*, 2013; Nilsson and Duan, 2018). The major primary bile acids synthesized in human liver are cholic acid (CDA) and chenodeoxycholic acid (CDCA), which are conjugated with taurine or glycine (T/G-CDA/CDCA) to increase their solubility. After their deconjugation, these molecules are converted by the gut microbiota into two hydrophobic species highly toxic, lithocholic and deoxycholic acids (LCA and DCA). The latter are excreted in feces (major pathway) or rapidly conjugated in low amount by sulfation, which is the major pathway for detoxification of hydrophobic bile acids in humans (Hofmann, 2004), to reach the liver. Some of LCA highly toxic derivatives include 12-ketolithocholic acid and tauroolithocholic acid (TLCA). Altogether, almost 95% of bile salts released in the gut lumen are reabsorbed and reach the liver through the portal vein (enterohepatic cycle of cholesterol) but a part is deconjugated or metabolized into secondary bile salts by the gut microbiota in the ileum and colon (Jia *et al.*, 2018; Wahlstrom *et al.*, 2016). *In vitro* models revealed that secondary bile acids stimulate inflammatory pathways such COX-2 (cyclooxygenase 2) and NF- κ B pathways (Glinghammar, 2002). Modulating dietary fat is a way to change the pool size and the profile of bile acids. In human, a high-fat diet rich in saturated fatty acids was associated with increased levels of luminal bile acids, and especially the most toxic bile acids, such as 12-ketolithocholic acid and TLCA (Murakami *et al.*, 2016; Wan *et al.*, 2020; Wang *et al.*, 2003). Conversely, a decrease in dietary fat amount may reduce the amount of bile acids released in the gut lumen, leading to a decrease in their metabolic transformation by the gut microbiota and thus limiting their potential adverse effects. Modifying the types of dietary fat may also induce significant modifications of the gut microbiota composition and function (bacterial enzymes) and hence bile acid profile. In addition to sulfation, which remains the major pathway for detoxification of hydrophobic bile acids in humans (Hofmann, 2004), the detoxification of bile acids by omega-3 PUFA has been recently proposed and demonstrated in hepatic and colonic human cells (Cieślak *et al.*, 2018). The authors showed that omega-3 PUFA reduce the expression of genes involved in bile acid synthesis and uptake in HepG2 cells, while activating genes encoding metabolic enzymes and excretion transporters. Omega-3 also reduced the hepatotoxicity by modifying the composition of the bile acid pool with less highly hydrophobic bile acids (Cieślak *et al.*, 2018). Further studies are thus needed to now investigate the additional impact of available lipid residues on the interaction of gut microbiota with bile acid metabolism and its influence on disease states.

4 Lipid emulsifiers and their impact on gut physiology

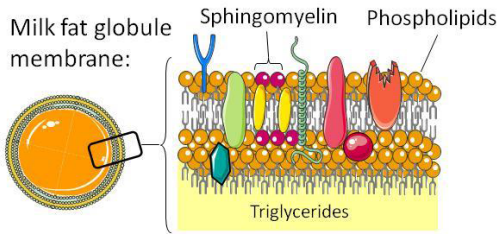
4.1 Synthetic and semi-synthetic emulsifiers

Fats and oils are in the emulsified state in many food products. As previously reported and reviewed, emulsification *per se* can result in enhanced intestinal lipid absorption and metabolic transformations in both preclinical and clinical models (Couëdelo *et al.*, 2017; Michalski *et al.*, 2017) and can also modulate the postprandial metabolic handling of LPS in obese men (Vors *et al.*, 2017). Importantly, emulsification involves the addition of emulsifiers and stabilizers in the food matrix to ensure both product stability and mouthfeel. In France, 15% of manufactured food products contain MAG and DAG (diglycerides) and their esters, 10% contain carrageenans (CGN), and 17% contain lecithins (Coudray *et al.*, 2019). Recent research has raised interest on the impact of these additives in the intestine and on metabolic health. Pioneering work by Chassaing *et al.* (2015) revealed that polysorbate 80 (PS80; E433) and carboxymethylcellulose (CMC; E466), when added in drinking water, can alter mouse gut microbiota and promote colitis and metabolic syndrome, involving mechanisms related to an altered mucus layer. Moreover, these synthetic emulsifiers can alter human gut microbiota composition *ex-vivo* and thereby potentiate intestinal inflammation (Chassaing *et al.*, 2017). In particular, CMC can directly impact the gene expression of proinflammatory molecules in gut bacteria, while PS80 modifies gut microbiota composition towards more proinflammatory species (Viennois and Chassaing, 2018). Milard *et al.* (2018a) investigated the impact of different common cream formulations in a 13% fat diet on mice intestine and metabolism after feeding periods of 1 or 4 weeks. Compared to a control cream devoid of additives, cream with k-CGN (E407)+MAG/DAG lactic esters (E471) increased the duodenal expression of genes involved in intestinal lipid absorption, tight junctions and endoplasmic reticulum stress after 1 week, but decreased *Muc2* gene expression. However, the cream containing these additives induced more mucus cells in the duodenum, jejunum and ileum after 4 weeks of diet, and the liver damage score was improved compared to mice fed the control cream (Milard *et al.*, 2018a). The longer-term impact and exact mechanisms by which these additives in foods impact the intestine and metabolism thus deserve to be further elucidated.

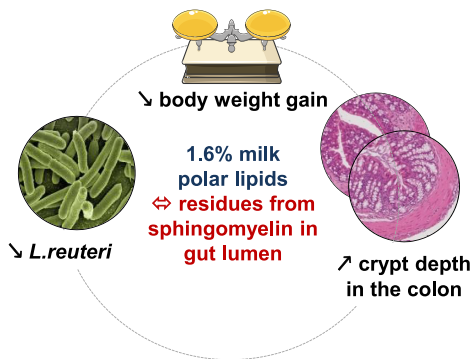
4.2 Polar lipids, relevant natural emulsifiers

Among food emulsifiers, polar lipids are interesting natural alternatives to synthetic additives. Soy lecithin (E322) is the most widely used polar lipid emulsifier and stabilizer. A recent review has summarized the impact of vegetable lecithins on lipid metabolism, and underlined the need to assess the extent to which they may also influence intestinal integrity, low-grade inflammation and gut microbiota (Robert *et al.*, 2020). Indeed, lecithin is the common name used for phosphatidylcholine, and gut bacteria possess a phospholipase activity producing diacylglycerols (DAG) from phospholipids (Morotomi *et al.*, 1990). Interestingly, the DAG production by intestinal bacteria is enhanced in the presence of bile acids (Morotomi

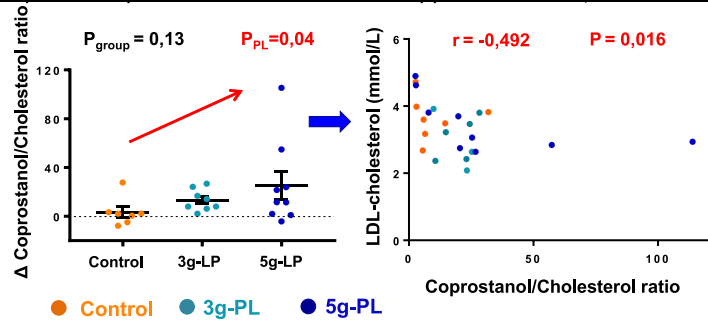
Milk polar lipids within the MFGM (Bourlieu and Michalski 2015):



In high-fat diet fed mice (Milard *et al.* 2019):



In postmenopausal women after 4 wk-supplementation (Vors *et al.* 2020):



In patients with ileostomy during meal digestion (Vors *et al.* 2020):

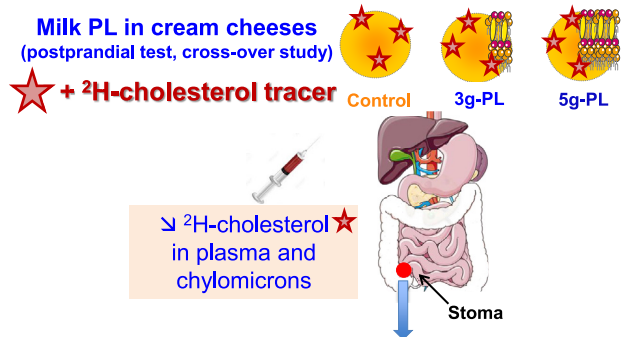


Fig. 3. Summary of the main recent findings of the authors relative to the impact of milk polar lipids on gut physiology in animal and human models. MFGM: milk fat globule membrane; PL: polar lipids.

et al., 1990). Given that DAG are bioactive molecules with key action on the protein kinase C (Morotomi *et al.*, 1990), more interest should be focused on such lipid metabolites in disease conditions.

Interest is currently growing on alternative sources of lecithin, notably milk polar lipids found in high concentrations in buttermilk and containing a high proportion (about ¼) of sphingomyelin (SM) (Bourlieu *et al.*, 2018). When incorporated at 1.2% in a semi-synthetic high-fat diet based on palm oil, soy lecithin enhanced adipose tissue hypertrophy and inflammation in mice compared to the high-fat diet devoid of polar lipids (Lecomte *et al.*, 2016). Conversely, milk polar lipids incorporated in a similar diet resulted in the same adiposity than control high-fat mice, but with a lower adipose tissue inflammation. Mice supplemented with milk polar lipids presented a lower endotoxemia and an increased number of colonic goblet cells indicating an improved gut barrier. A possible mechanism could involve residues of milk SM that reached the colon because increased amount of C22:0 to C24:0 fatty acids, typical of milk SM species, were detected in mice feces. Other recent studies confirmed that milk SM is able to decrease endotoxemia in mice (Norris *et al.*, 2016). In the context of both low-fat and high-fat diets, milk SM can also increase the abundance in mice gut microbiota of Bifidobacteria (Norris *et al.*, 2016, 2019), known to be associated with lower endotoxemia and improved gut barrier integrity (Cani *et al.*, 2008). Moreover, milk SM was reported to increase the expression of tight junction proteins in Caco-2 intestinal cells (Milard *et al.*, 2018b). When added in a high-fat diet based on chow, 1.6% milk polar lipids impact gut physiology by

increasing colonic crypt depth and changing the composition of the bile acid pool present in the gallbladder, decreasing the amount of more hydrophobic species and thus reducing bile salt hydrophobicity (Milard *et al.*, 2019) (Fig. 3). This was associated with a decreased abundance of *Lactobacillus* spp. and notably *Lactobacillus reuteri* (*Limosilactobacillus reuteri* in the new taxonomy), which had otherwise been described as associated with weight gain and decreased ileal crypt depth (Milard *et al.*, 2019). Strikingly, the abundance of these bacteria of interest in mice feces was negatively correlated with the fecal loss of fatty acids specific of milk SM. This resulted in a wider metabolic impact as the 1.6% milk polar lipid diet decreased body weight gain and reduced adiposity compared to the high-fat diet devoid of polar lipids (Milard *et al.*, 2019) (Fig. 3).

Altogether, the beneficial effects of milk polar lipids on hyperlipemia and cardiovascular risk were reported previously in mouse models but were still controversial in humans. In this context, we demonstrated recently for the first time in humans that the 4-week consumption of 5 g/day of milk polar lipids incorporated in a cream cheese improved several key lipid markers of cardiovascular risk in postmenopausal women, by decreasing LDL-cholesterol (-8.7%), serum TAG (-15%), ApoB/ApoA1 ratio (-6.7%) and increasing HDL-cholesterol (+5%) compared to control cream cheese containing milk TAG only (Vors *et al.*, 2020). This lipid-lowering effect of milk polar lipids was associated with an increased proportion of fecal coprostanol, a non-absorbable metabolite of cholesterol produced by specific gut bacteria (Fig. 3). The fecal coprostanol/cholesterol ratio also correlated negatively with

the decrease of LDL-cholesterol and total cholesterol (Fig. 3). We further reported that the mechanisms can be due to the increased excretion of both undigested milk SM residues (~20% of ingested dose) and cholesterol (both exogenous and endogenous) at the end of the small intestine by investigating postprandial tests in volunteers with ileostomy (Vors *et al.*, 2020) (Fig. 3). Such results demonstrate that milk polar lipids can beneficially impact cardiometabolic health and metabolism through the action of specific lipid residues in the gut. Recent preclinical studies revealed that milk polar lipids attenuate atherosclerosis development in LDL-receptor knockout mice (Millar *et al.*, 2020) and the wider health benefits of milk polar lipids have just been reviewed (Anto *et al.*, 2020). Therefore, how different plant-based and animal sources of polar lipids may impact the gut and the related metabolic health in the context of food formulation deserves further investigations (Robert *et al.*, 2020).

5 Conclusion and future prospects related to the food matrix

Altogether, recent research supports the need to deeper explore the fate of dietary lipids along the gastrointestinal tract. Residual lipids reaching the colon can exert their own effects on the gut microbiota and intestinal mucosa, or *via* specific lipid metabolites after metabolic transformations by gut microorganisms, which remains to be deeper understood. The impact of specific bioactive lipids including phospholipids and sphingolipids is notably a topic of current interest (Le Barz *et al.*, 2020; Robert *et al.*, 2020). Moreover, the causal link between dietary lipid impacts in the gut and their metabolic effects is a timely issue. In this respect, recent research support the food matrix concept, whereby the metabolic impact of nutrients vary according to the food source. This has been supported by recent articles regarding different food sources of saturated fatty acids (Mozaffarian *et al.*, 2011; de Oliveira Otto *et al.*, 2012; Wu *et al.*, 2019). This is notably relevant for the dairy matrix in the context of cardiometabolic risk prevention, whereby the effects of full fat dairy are not those expected considering their fatty acid profile only (Astrup, 2014; Drouin-Chartier *et al.*, 2016). Part of the mechanisms may involve cheese content in MFGM and the milk polar lipids within, notably *via* their impacts in the intestine as reported in the present review. Other proposed mechanisms are related to the fact that different dairy matrixes induce differential release of nutrients, and notably lipids, along the gut (Thorning *et al.*, 2017). This new paradigm is also relevant for plant-based foods, as lipids trapped in seed oleosomes can partly escape digestion and be found down to the colon where they may exert effects on gut physiology and wider health impacts (Ellis *et al.*, 2004; Grundy *et al.*, 2015). In the recent context of transition towards more plant-based food sources (Magkos *et al.*, 2020), it is now important to decipher how natural *versus* formulated food matrixes, and how natural lipid additives of plant-based *versus* animal origin, impact gut physiology and metabolic health.

Competing interests

Marie-Caroline Michalski coordinated a project aiming to valorize nutritional properties of milk polar lipids from

buttermilk, funded by ANR (ANR-11-ALID-007-01, VALO-BAB), in which C. Vors was involved. M.-C.M. received research fundings from Sodiaal-Candia R&D, the Centre National Interprofessionnel de l'Economie Laitière (CNIEL, French Dairy Interbranch Organization) and Nutricia Research. The present review was not part of these projects. M.-C. M. is an external expert member of the Scientific Committee of ITERG and is a member of UMT ACTIA BALI (BioAvailability of Lipids and Intestine). The present review was not part of these activities.

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