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## LIPID CONSUMPTION AND FUNCTIONALITY: NEW PERSPECTIVES CONSOMMATIONS ET FONCTIONNALITÉS DES LIPIDES : NOUVEAUX HORIZONS

### Dietary lipid emulsions and endotoxemia

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**Abstract** – The low-grade inflammation observed in obesity is a risk factor for cardiovascular diseases and insulin resistance. Among factors triggering such inflammation, recent works revealed the role of bacterial lipopolysaccharides (LPS), so-called endotoxins. LPS are naturally present in the gut *via* the intestinal microbiota. Recent studies show that they can induce in plasma a metabolic endotoxemia after the consumption of unbalanced hyperlipidic meals. This article reviews recent knowledge gained on the role of intestinal lipid absorption and the composition of dietary lipids on: (i) the induction of metabolic endotoxemia, (ii) the types of plasma transporters of LPS and (iii) associated low-grade inflammation. Notably, lipids are present in foods under various physicochemical structures and notably in emulsified form. Our recent works reveal that such structure and the type of emulsifier can modulate postprandial lipemia; recent results on the possible consequences on metabolic endotoxemia will be discussed.

**Keywords:** Nutrition / fat / oil / emulsifier / inflammation

**Résumé** – **Émulsions lipidiques alimentaires et endotoxémie.** L'inflammation à bas bruit observée en situation d'obésité représente un facteur de risque cardiovasculaire et d'insulinorésistance. Parmi les facteurs responsables de cette inflammation, des travaux récents ont révélé l'implication des lipopolysaccharides bactériens, aussi appelés endotoxines. Ces endotoxines sont naturellement présentes dans le tractus digestif *via* le microbiote intestinal. Des études récentes montrent qu'elles peuvent générer une endotoxémie métabolique dans le plasma suite à la consommation de repas déséquilibrés hyperlipidiques. L'objectif de cette revue est de faire le point sur les connaissances récentes concernant le rôle de l'absorption intestinale des lipides et de la composition de ces derniers sur : (i) l'établissement d'une endotoxémie métabolique, (ii) la qualité des transporteurs plasmatiques des LPS et (iii) l'inflammation à bas bruit associée. En particulier, les lipides sont présents dans les aliments sous différentes structures physico-chimiques et notamment sous forme émulsionnée. Nos travaux récents montrent que cette structure est à même de moduler la lipémie postprandiale. Des résultats récents sur les possibles conséquences sur l'endotoxémie métabolique sont discutés.

**Mots clés :** Nutrition / matière grasse / huile / émulsifiant / inflammation

## 1 Introduction

Metabolic diseases such as obesity and type 2 diabetes result from genetic, environmental and nutritional factors. They are characterized by the set up and maintenance of a low-grade inflammatory status, which increases cardiovascular risk (Libby, 2002; Ross, 1999). Low-grade inflammation is revealed by the increased plasma concentration of several mediators including proinflammatory cytokines such as IL-6 and TNF- $\alpha$ , and adipokines as MCP-1, albeit in much lower concentrations than usually observed in a general inflamma-

tory reaction as in septic shock (Blackwell and Christman, 1996). These inflammatory phenomena are currently the focus of numerous researches in nutrition and health because they are strongly involved in the development of obesity-associated metabolic disorders: type 2 diabetes, insulin resistance, atherosclerosis, etc.

However, the origin of metabolic inflammation development remains poorly solved. In altered metabolic state, two types of inflammatory phenomena can occur (Ding and Lund, 2011; Laugerette *et al.*, 2011): chronic metabolic inflammation or so-called “low grade inflammation”, and transient inflammation described in the postprandial phase; or so-called “postprandial inflammation” contributing to maintain the chronic low-grade inflammation.

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On a nutritional point of view, the impact of dietary lipids in these phenomena has gained growing interest and results are sometimes conflicting. In healthy, overweight or diabetic subjects, a hypercaloric meal notably with excessive fat content (50 g lipids corresponding to 59.2% of total energy intake (TEI) from sausage, bread, egg, butter and olive oil) increase inflammatory cytokines conversely to a carbohydrate-rich pizza-based meal (Nappo *et al.*, 2002). Moreover, in coronary disease patients, a meal with 65 g of lipids (including soybean-oil based dressing) results in the postprandial increase of plasma IL-6 concentration (Lundman *et al.*, 2007). Moreover in rats, a role of the visceral adipose tissue in postprandial inflammation was shown, notably with an transient increase of the activation of transcription factor NF- $\kappa$ B (Magné *et al.*, 2010).

However, the nutritional mechanisms leading to the development of low-grade inflammation are not fully elucidated. Recent studies show that the intestinal microbiota can be involved. It is now widely known that the composition of intestinal microbiota differs between normal-weight and obese humans, notably with a lower diversity of bacterial species in obesity (Furet *et al.*, 2010; Ley, 2010; Ley *et al.*, 2006; Zhang *et al.*, 2009).

Recent studies revealed that proinflammatory molecules of bacterial origin, naturally present in the intestinal microbiota and thus in the gut, can reach the bloodstream. These are endotoxins (lipopolysaccharides, LPS), whose plasma concentration and/or activity (endotoxemia) is increased in obese people (Libby, 2002), type 2 diabetics (Creely *et al.*, 2007) and patients with Crohn's disease (Pastor Rojo *et al.*, 2007). Moreover, in ob/ob mice lacking the leptin gene and fed a high-fat diet, antibiotic treatment modifies the gut microbiota and lowers endotoxemia (Cani, Rottier *et al.*, 2008). In humans, consumption of yogurt containing probiotics improved gut barrier and lowered endotoxemia, resulting in decreased metabolic inflammation (Schiffrin *et al.*, 2009). More recently, endotoxemia was reported to be highly correlated with the number of components of the metabolic syndrome (Lassenius *et al.*, 2011).

Altogether, these studies raise the question about the role of dietary lipids in the modulation of metabolic inflammation via intestinal microbiota and the role of endotoxin passage in plasma, which is the topic of this review.

## 2 Endotoxins are proinflammatory molecules

Endotoxins (LPS) constitute 80% of Gram negative bacteria cell wall. Their structure contain a polysaccharide part, the O-specific chain (so-called antigen O) and a lipid part, the lipid A, which is a highly conserved region representing the toxic part of LPS (Osborn *et al.*, 1964). Bacterial LPS are inflammatory molecules, *i.e.*, induce proinflammatory signaling pathways (Fig. 1). Endotoxemia is measured as the endotoxin activity using the Limulus Amoebocyte Lysate test, validated by the European Pharmacopea. It is increasingly used in metabolic studies and therefore was adapted to the plasma of different species to this aim (Laugerette *et al.*, 2015). Of note, emerging methods aim at quantifying LPS molecules *via*

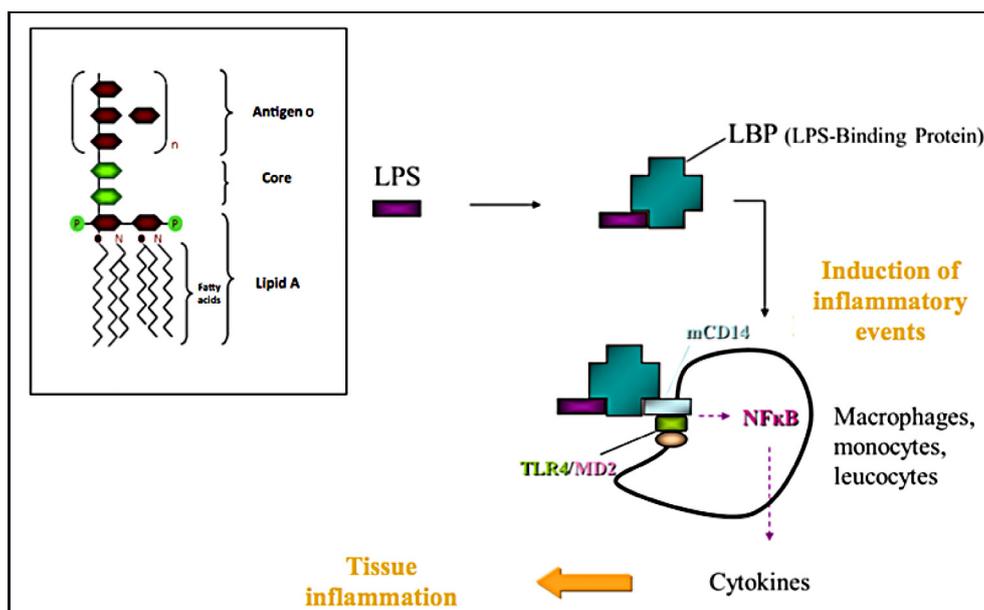
the analysis of 3-hydroxymuramic acid from their lipid A in plasma (Pais de Barros *et al.*, 2015).

If reaching the bloodstream, LPS are taken up by a specific transport protein: the lipopolysaccharide-binding protein (LBP, 60 kDa), secreted mostly by the liver but also by the white adipose tissue (Moreno-Navarrete *et al.*, 2013) and present in plasma at concentrations in the range of 2–20  $\mu$ g/ml (usually  $\sim$ 18  $\mu$ g/ml in humans) (Gallay *et al.*, 1994). LPS are then transferred to the CD14 receptor (cluster of differentiation 14; Fig. 1), which exists in 2 forms: a membrane form (mCD14) expressed at the membrane of numerous cells (notably macrophages, monocytes etc.) (Hailman *et al.*, 1994), and a soluble form expressed by cells lacking mCD14 such as endothelial cells (Bazil and Strominger, 1991). LBP and sCD14 are considered as markers of endotoxin exposure in plasma (Hiki *et al.*, 1999), because their half-lives (24–48 h) are longer than that of LPS (< 8 min in mice and up to 3 h in humans) (Matsushita *et al.*, 2010; Pastor Rojo *et al.*, 2007). Moreover, the ratio LBP/sCD14 is increased in some inflammatory diseases such as Crohn's disease (Lakatos *et al.*, 2011). On a metabolic standpoint, both forms of CD14 are able to bind the LPS-LBP complex, which can then fix on the TLR4 receptor (toll-like receptor 4) and the co-receptor MD2 (myeloid differentiation protein-2) and then mediate signal transduction *via* the activation of NF- $\kappa$ B (Nuclear Factor- $\kappa$ B). This signalization cascade results in the secretion of proinflammatory cytokines (IL-6, TNF- $\alpha$ , IL-1 $\beta$ , etc.) (Fig. 1).

Notably, during a septic shock, LBP can transfer LPS to plasma lipoproteins (HDL, chylomicrons), which allows to neutralize endotoxin activity (Eichbaum *et al.*, 1991; Harris *et al.*, 1993; Vreugdenhil *et al.*, 2003). This neutralization results from the link of lipoproteins to their receptors notably in the liver, inducing LPS clearance with bile secretion (Eichbaum *et al.*, 1991; Harris *et al.*, 1993, 1998; Vreugdenhil *et al.*, 2003). Not only LBP but also the phospholipid transfer protein (PLTP) can bind LPS and contribute to detoxification during septic shocks (Gautier *et al.*, 2008).

## 3 Links between endotoxemia and metabolic diseases

In the context of unbalanced hypercaloric diets, LPS naturally present in the gut can induce metabolic endotoxemia in the long term, thereby actively participating in maintaining metabolic inflammation related to obesity (Kelly *et al.*, 2012; Kemp, 2013). Indeed, pioneering mice studies revealed that the gut microbiota acts as a “tank” of endotoxins that can increase in plasma after a fat-rich meal and induce inflammation (Cani *et al.*, 2007). This so-called “metabolic endotoxemia”, conversely to the usual septic shock endotoxemia, was closely related to changes in the composition of gut microbiota (Cani, Bibiloni *et al.*, 2008). The proof-of-concept studies showed that 4 weeks of lard-based high fat diet in mice (72% of TEI) increases endotoxemia unlike the control chow diet. Endotoxemia induced by this high fat diet was increased 2.7-fold (Cani, Amar *et al.*, 2007). Moreover, chronic infusion of low amounts of LPS, similar to those observed after the high fat diet, in chow-fed mice led to increased weight gain



**Fig. 1.** Pro-inflammatory events induced by plasma lipopolysaccharides (LPS). Adapted from Laugerette *et al.* (2011); Vors *et al.* (2014). If reaching the bloodstream, LPS are taken up by a specific transport glycoprotein, the lipopolysaccharide-binding protein (LBP), towards immune cells (such as macrophages). Immune cell activation requires a specific molecular complex consisting of the membrane form of the cluster of differentiation 14 (mCD14), the Toll-Like Receptor 4 (TLR4) and the Myeloid Differentiation protein-2 (MD2). The mCD14 is a glycoprotein able to bind the LPS-LBP complex, which can then fix on the TLR4 receptor and the co-receptor MD2 and then mediate signal transduction via the activation of NF- $\kappa$ B (Nuclear Factor- $\kappa$ B). This signaling cascade results in the secretion of proinflammatory cytokines (IL-6, TNF- $\alpha$ , IL-1 $\beta$ , etc.).

and insulin resistance. However, CD14-KO mice did not develop weight gain and insulin resistance when fed the high fat diet (Cani *et al.*, 2007). Moreover, the increase of endotoxemia was lower (1.4-fold compared with chow-fed mice) when mice were fed a moderate high fat diet with 40% of total energy intake (TEI) as lipids instead of 72% (Cani *et al.*, 2007).

Some reports highlight that increased endotoxin absorption can be triggered by an increase of intestinal permeability (Cani, Bibiloni *et al.*, 2008; de La Serre *et al.*, 2010). Among factors involved in increased intestinal permeability are reported (i) an altered composition of the gut microbiota (Cani and Delzenne, 2010), notably a dysbiosis characterized with decreased bacterial diversity (Le Chatelier, 2013), and (ii) the chronic consumption of lipid-rich palatable foods (Frazier *et al.*, 2011). Both factors are observed in obesity, which could explain the greater intestinal permeability in obese rodents as well as a higher fasting metabolic endotoxemia.

Links have also been described between endotoxemia, lipid metabolism and weight gain. In humans, recent studies showed that plasma endotoxemia was higher in obese subjects with type 2 diabetes (Creely *et al.*, 2007) and in patients suffering from inflammatory gut diseases (Pastor Rojo *et al.*, 2007) compared with healthy controls. Increased intestinal permeability is also associated with visceral adiposity in otherwise healthy women (normal-weight and overweight) (Gummeson *et al.*, 2011). Moreover, increased plasma endotoxemia was associated with higher food intake and correlated notably with higher fat intake in healthy subjects with metabolic and cardiovascular risk factors (Amar *et al.*, 2008). More recently, endotoxin activity was highly correlated with the different components of metabolic syndrome (Lassenius *et al.*, 2011).

#### 4 Intestinal lipid absorption contributes to the translocation of endotoxins in the bloodstream

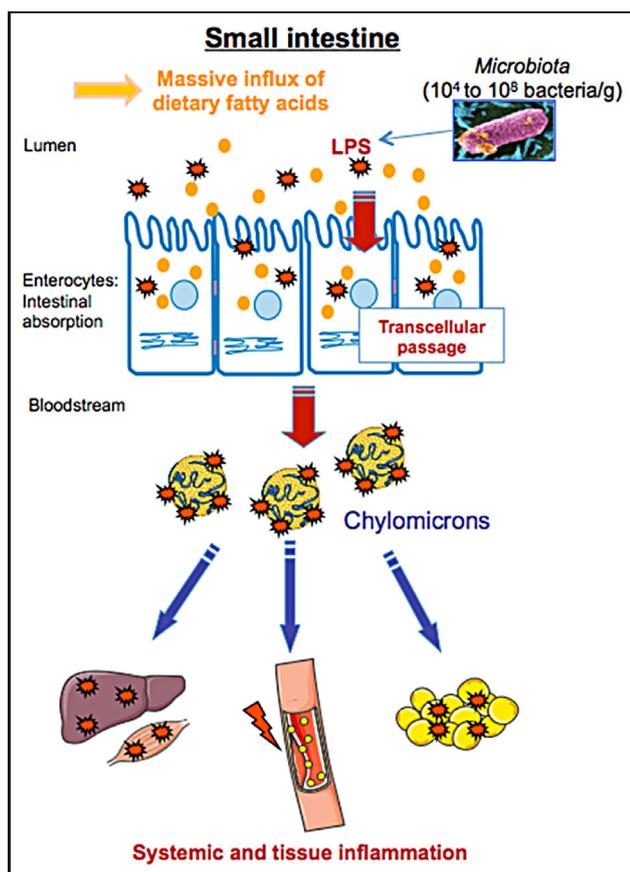
The postprandial phase has recently been shown to contribute to metabolic endotoxemia due to the co-absorption of LPS with dietary lipids. In fact endotoxins present in the gut due to the lysis of Gram negative bacteria may reach the bloodstream in the postprandial phase by different means: (i) by absorption by the intestinal mucosa during lipid absorption (Cani *et al.*, 2007; Erridge *et al.*, 2007; Ghanim *et al.*, 2009; Laugerette *et al.*, 2011, 2012) (transcellular passage, shown in humans, in rodents and *in vitro*), (ii) by passive diffusion due to increased intestinal permeability (paracellular passage, shown in rodents) (Cani, Bibiloni *et al.*, 2008), (iii) by bacterial translocation from the gut through intestinal mucosa to peripheral organs (Neal *et al.*, 2006) (shown *in vitro* and in rodents).

Even if it was the most recently described, the phenomenon of postprandial endotoxemia has already been shown in several studies in humans. Table 1 reports the composition of tested meals and major conclusions of these studies (Vors *et al.*, 2014). A first human study revealed that in lean to obese subjects, occasional smokers, a meal containing toasts with 50 g of butter (41 g of fat) was sufficient to transiently induce endotoxemia 30 min after meal ingestion (Erridge *et al.*, 2007). The mechanism of co-absorption lipids/endotoxins consists in a facilitated transport of LPS by chylomicrons secreted in plasma during lipid digestion (Ghoshal *et al.*, 2009; Laugerette *et al.*, 2011) (Fig. 2). In mice 90 min after gavage with a bolus of triolein, plasma endotoxemia increased, conversely to a

**Table 1.** Effect of test meal composition on postprandial endotoxemia in human studies. Adapted from Vors *et al.* (2014).

References	Subjects	Dairy-based test meals		Effect on endotoxemia
		Energy ( <i>E</i> ) and macronutrients	Food	
Erridge <i>et al.</i> , 2007	Healthy, normal-weight to obese ( <i>n</i> = 12); M	Total <i>E</i> : ~900 kcal	1 cup of tea and 3 slices of toast spread with a total of 50 g butter	Transient increase in plasma LPS concentrations: postprandial peak 30 min after meal.
Deopurkar <i>et al.</i> , 2010	Healthy, normal-weight ( <i>n</i> = 4 × 12)	Total <i>E</i> : 300 kcal	75 g of glucose or 75 g of cream (33 g of lipids: 70% SFA, 28 % UFA) or an equicaloric amount of orange juice, or 300 ml of water	Significant increased endotoxemia after the intake of cream at 3 h (45 ± 17% over the baseline) but not after glucose, orange juice, or water intake. Postprandial LPS concentrations after the intake of cream significantly higher than basal levels up to 5 h.
Harte <i>et al.</i> , 2012	Healthy controls ( <i>n</i> = 9), obese subjects ( <i>n</i> = 15), and patients with impaired glucose tolerance ( <i>n</i> = 12) and type 2 diabetes ( <i>n</i> = 18)	Total <i>E</i> : ~700 kcal; 75 g fat, 5 g carbohydrate, 6 g protein	Whipping cream	Significant rise in endotoxin levels <i>vs.</i> baseline in obese subjects, patients with impaired glucose tolerance and type 2 diabetes over the 4-h time period.
Vors <i>et al.</i> , 2015	Healthy, normal-weight ( <i>n</i> = 8) and non insulin-resistant obese ( <i>n</i> = 8) subjects; M	Total <i>E</i> : 282 kcal for 10 g fat-breakfast and 551 kcal for 40 g fat-breakfast	Anhydrous milk fat with bread and a glass of skim milk	Only obese had higher postprandial endotoxemia after 40 g of fat <i>vs.</i> 10 g fat. Chylomicrons of obese subjects got more enriched with LPS than those of normal-weight along the postprandial phase.
References	Subjects	Mixed test meals		Effect on endotoxemia
		Energy ( <i>E</i> ) and macronutrients	Food	
Laugerette <i>et al.</i> , 2011 Laugerette <i>et al.</i> , 2014	Healthy, normal-weight to overweight ( <i>n</i> = 12); M	Total <i>E</i> : 291 kcal; 33 g fat	200 ml of Fortimel® (enteral emulsion), 23 g of margarine, 9.4 g of butter, 1 g of olive oil, 85 g of bread, 20 g of jam and 200 g of banana	Transient increase in postprandial plasma endotoxin concentration, with a hint of a peak at 60 min. At this peak time, endotoxemia tended to be higher in the chylomicron fraction. Higher increase of postprandial endotoxemia after 8 weeks of overfeeding.
Ghanim <i>et al.</i> , 2009	Healthy, normal-weight ( <i>n</i> = 10); M	Total <i>E</i> : 910 kcal ; 51 g fat (among which 33% SFA), 88 g carbohydrate, 34 g protein	Egg muffin and sausage muffin sandwiches and two hash browns	Postprandial LPS concentration increase of 47 ± 14% over the baseline at 3 h.
Ghanim <i>et al.</i> , 2010	Healthy, normal-weight ( <i>n</i> = 3 × 10); M/W	900 kcal (51 g fat, 81 g carbohydrate, 32 g protein) + 75 g glucose (300 kcal) or orange juice or water	Egg muffin and sausage muffin sandwiches and two hash browns + an extra 350 ml water with the glucose drink	Postprandial LPS concentration increase of 70 ± 21% over the baseline at 3 h after high-fat high-glucose meal. Postprandial LPS concentration increase of 60 ± 216% over the baseline at 5 h after high-fat meal with water. No increase of endotoxemia after high-fat meal with orange juice.
References	Subjects	Basic lipid load		Effect on endotoxemia
		Energy ( <i>E</i> ) and macronutrients	Food	
Clemente-Postigo <i>et al.</i> , 2012	Morbidly obese with insulin resistance ( <i>n</i> = 40)	50 g fat including 10 g SFA, 30 g MUFA and 10 g PUFA	Oral fat load (100 ml)	Increased plasma- and chylomicron-endotoxemia at 3 h.

M/W: men/women; SFA: saturated fatty acids; UFA: unsaturated fatty acids. MUFA: monounsaturated fatty acids; PUFA: polyunsaturated fatty acids.



**Fig. 2.** Postprandial endotoxemia and associated inflammation induced by the intestinal transcellular passage of bacterial LPS during lipid absorption (adapted from Vors *et al.*, 2014). During a massive influx of dietary fatty acids in the postprandial phase, the LPS originated from the small intestine can be absorbed thanks to a transcellular passage during the intestinal absorption of dietary lipids. LPS are then transported in the bloodstream thanks to chylomicrons secreted in the postprandial phase. The circulating LPS are then partially taken up by specific transport proteins as described in Figure 1, therefore generating inflammatory events in the vascular endothelium and peripheral tissues.

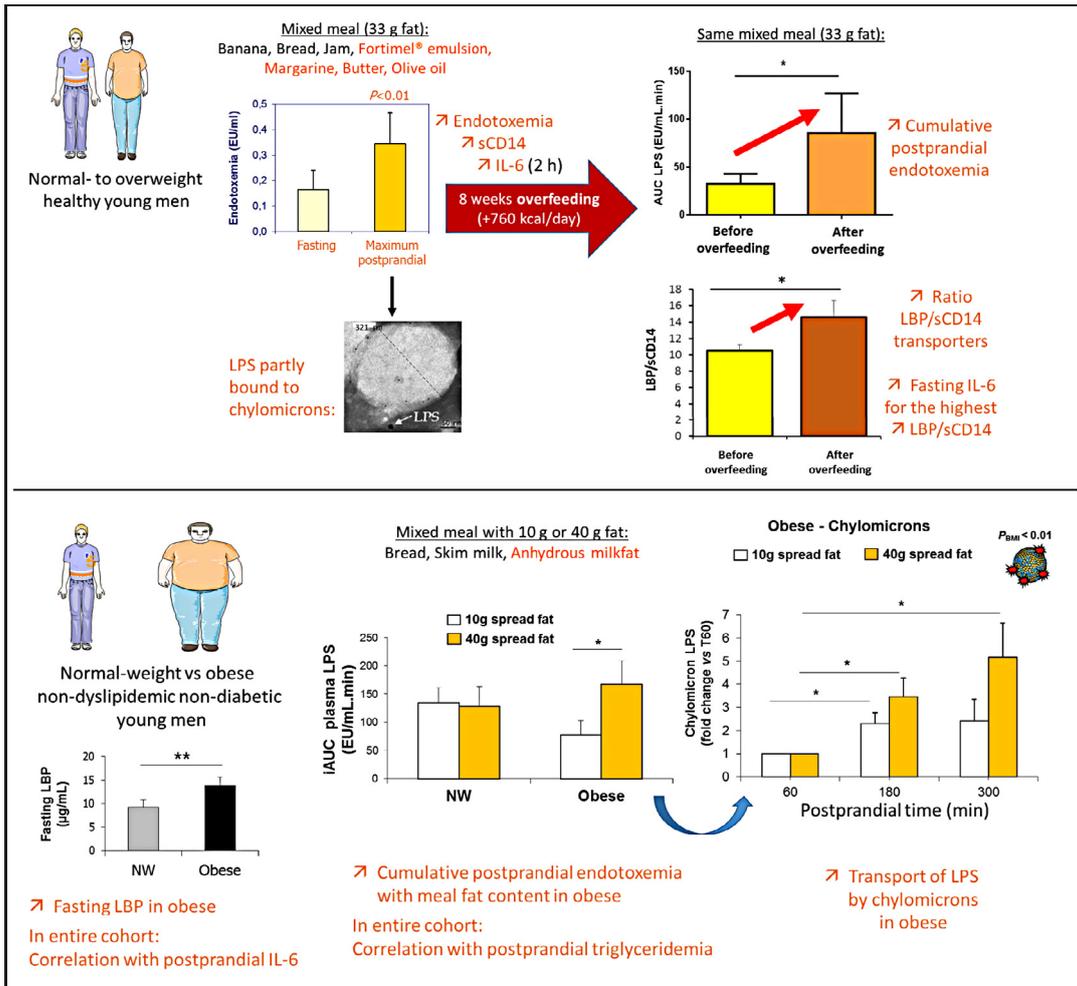
gavage with tributyrin, a short-chain triglyceride that do not induce chylomicron secretion, or after a chemical product that blunts chylomicron secretion (Ghoshal *et al.*, 2009). Moreover, different studies in healthy and lean humans showed an increase of plasma LPS in the postprandial phase after ingestion of fat-rich meals, with or without carbohydrates (Deopurkar *et al.*, 2010; Ghanim *et al.*, 2010) (Tab. 1). More recently, we showed that the digestion of a mixed meal containing 33 g of lipids from different sources (margarine, butter, olive oil) by healthy non-smoking normal to overweight men, induced a transient increase of postprandial endotoxemia and sCD14 (Fig. 3). This was followed by a peak of proinflammatory cytokine IL-6 at 2 h after the meal (Laugerette *et al.*, 2011). Importantly, isocaloric loads of glucose or orange juice, or water, do not induce postprandial endotoxemia (Deopurkar *et al.*, 2010). Moreover, electronic microscopy and LAL analyses revealed that LPS were partly transported by chylomicrons (Laugerette *et al.*, 2011). Interestingly, 8 weeks of overfeed-

ing (+760 kcal/day as butter, almonds and Emmental cheese) in this cohort resulted in enhancing the postprandial endotoxemia 1.6-fold (Laugerette *et al.*, 2014). Mixed hyperlipidic/hyperglucidic meals (51 g lipids, 81 g carbohydrates) also increase plasma LPS in the postprandial phase in healthy lean men (Ghanim *et al.*, 2009, 2010). Recent studies confirm these results of postprandial endotoxemia in type 2 diabetic subjects consuming 75 g of lipids (Harte *et al.*, 2012) and in morbidly obese subjects consuming a 50 g lipid load (Clemente-Postigo *et al.*, 2012). Among postprandial studies, some used dairy fat (butter or cream), other used mixed fat-rich foods (often eggs and sausage) or simple oil load or, in the form of single food or into mixed meals, and altogether fat intake was high (Tab. 1). Most recently, we showed that increasing fat amount from 10 g to 40 g in a realistic mixed meal (milkfat, bread and skimmed milk) resulted in similar cumulative postprandial endotoxemia in normal-weight healthy men. In contrast, the 40 g-fat meal resulted in a higher cumulative postprandial endotoxemia than the 10 g-fat meal in healthy obese men, associated with an enhanced enrichment of chylomicrons with LPS along the postprandial phase compared to normal-weight subjects (Vors *et al.*, 2015). Therefore, postprandial endotoxemia is modulated by ingested fat amount in obese men, partly through a different LPS handling in plasma by chylomicrons (Fig. 3).

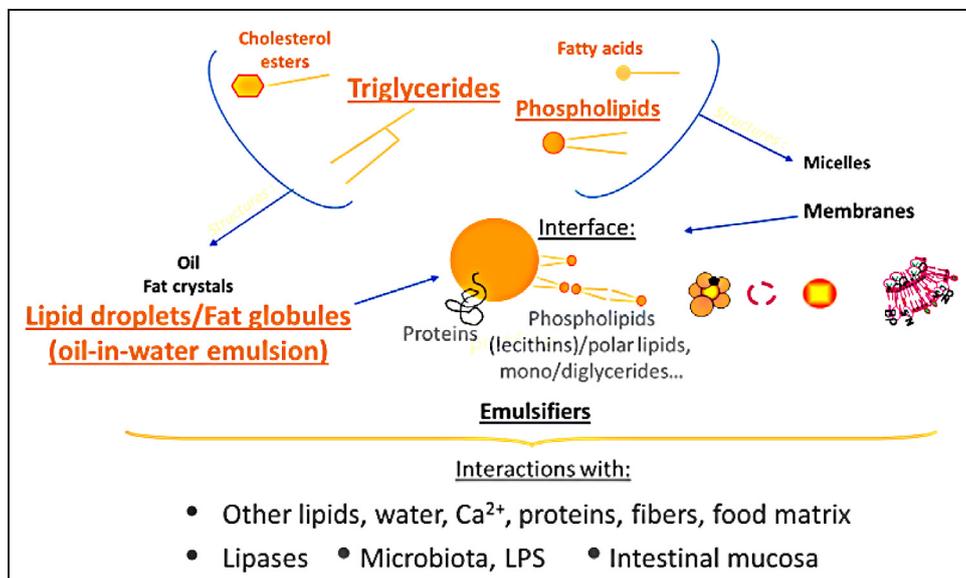
Altogether, unbalanced diets notably rich in lipids result in increased endotoxemia, notably via the repeated postprandial phases, which can contribute to the development of low-grade inflammation. However, dietary lipids are various in chemical nature and physico-chemical organizations in foods: different fats and oils exist, and each one can be formulated as bulk or more or less emulsified structures, with the use of different emulsifying agents such as proteins or phospholipids (Fig. 4). The impact of these varieties of lipid structures on lipid absorption and endotoxemia is an emerging research field (Bourlieu and Michalski, 2015; Michalski *et al.*, 2013).

## 5 Oil composition, emulsified structure and dietary emulsifiers can modulate endotoxemia and associated inflammation

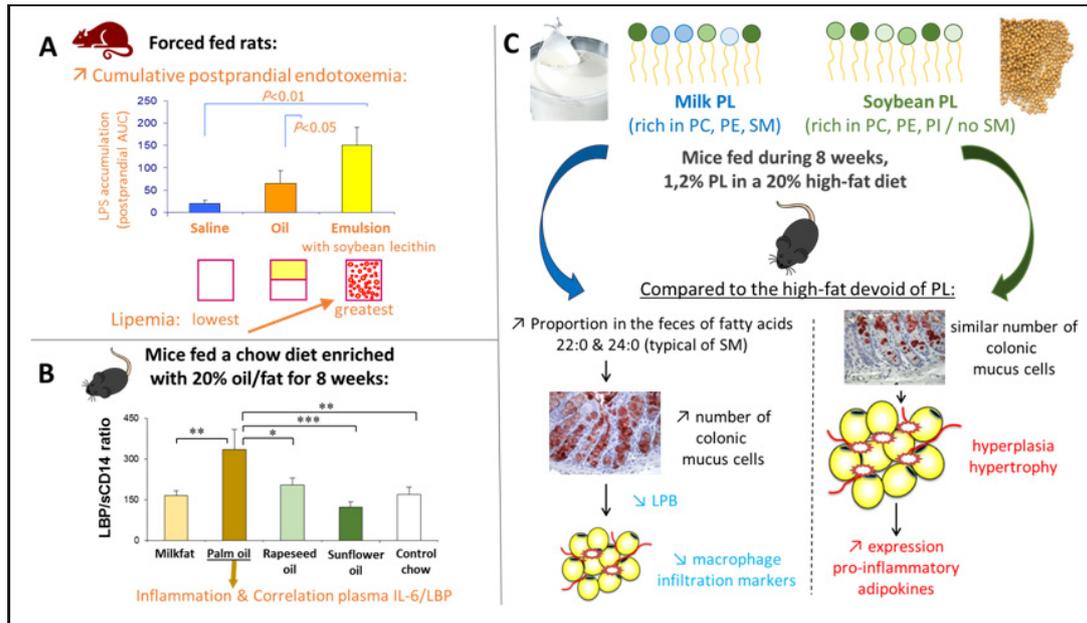
Several studies showed that metabolic endotoxemia can result from intestinal absorption of LPS due to a high fat meal, however, nothing was known until recently about the impact of fats and oils composition on endotoxemia. Moreover, most rodent studies used synthetic diets characterized by a % of TEI as fat greater than 60% and mostly based on lard and devoid of carbohydrates (Cani *et al.*, 2007). Therefore, we designed a study to compare the impact of different oils on long-term markers of endotoxemia and associated metabolic inflammation. Mice were fed during 8 weeks with 4 different high fat diets enriched with either milk fat, refined non-hydrogenated palm oil, rapeseed oil or sunflower oil. Energy intake as fat was similar to occidental diets, namely ~38% (*i.e.* ~20 wt% in the diet); oils were incorporated in mice chow diet that is mostly based on cereals and soy and fish proteins. Altogether, the palm oil diet resulted in the greatest inflammatory outcome associated with higher LPS transporter



**Fig. 3.** Summary of recent studies about postprandial endotoxemia in lean, overweight or obese men (Laugerette *et al.*, 2011, 2014; Vors *et al.*, 2015). Upper panel: lean to overweight subjects were submitted to the same postprandial test before and after 8 weeks of overfeeding. Lower panel: lean and obese subjects were submitted to two different postprandial tests varying by the amount of fat in the meal.



**Fig. 4.** Examples of supramolecular organization of lipid molecules in food products, oil-in-water emulsions and emulsifiers, which can impact on digestive and postprandial events. Adapted from Michalski *et al.* (2013).



**Fig. 5.** Summary of recent studies about the impact of oil composition, emulsified structure and the type of phospholipid emulsifier on endotoxemia and inflammation (Laugerette *et al.*, 2011, 2012; Lecomte *et al.*, 2016). (A) Catheterized rats were forced fed with saline, sunflower oil + saline or an emulsion of sunflower oil in saline using soybean phospholipids (lecithin) as emulsifier and blood was drawn along the postprandial phase. (B) Mice were fed with high-fat diets varying in fat source during 8 weeks and different markers of endotoxemia and inflammation were measured in plasma and adipose tissue. (C) Mice were fed with a synthetic high-fat diet based on palm oil during 8 weeks, or with a modified diet in which 1.2% of the triglycerides have been replaced with 1.2% of polar lipids (PL, mainly phospholipids) from either milk or soybean. PC: phosphatidylcholine, PE: phosphatidylethanolamine, PI: phosphatidylinositol, SM: sphingomyelin.

LBP, while the rapeseed oil diet resulted in lower inflammation and LBP (Laugerette *et al.*, 2012). We showed that mice fed the palm oil diet presented the highest plasma IL-6 concentration with an increased expression of pro-inflammatory cytokine IL- $\beta$  and of LPS receptors TLR4 and CD14 in the white adipose tissue (Laugerette *et al.*, 2012). This increased inflammation in the palm group was also associated with an increased proportion of *E. coli* (Gram negative bacteria thus containing LPS) in the gut microbiota. In contrast in the white adipose tissue of the group fed with the rapeseed oil diet, a lower expression of inflammation markers and LPS receptors was observed. Our study shows that the lipid composition of the diet can differently modulate the inflammatory outcome related to endotoxin metabolism. Recent acute studies show that this can be partly explained by differences in postprandial endotoxemia according to oil composition. Pigs were fed a meal dough enriched with 50 g of different oils: the lowest cumulative postprandial endotoxemia was measured after fish oil and the highest after coconut oil; while intermediate endotoxemia was observed after a vegetable oil (unspecified containing 50% arachidonic acid, 32% oleic acid and 13% palmitic acid) (Mani *et al.*, 2013). This difference could be explained by the apparent intestinal permeability to LPS, measured on ileon ex-vivo in Ussing chambers using FITC-LPS, which was highest in the coconut oil group and lowest in the fish oil group (Mani *et al.*, 2013). Altogether, oil composition can modify acute and long-term endotoxemia in different animal models, which would now deserve to be confirmed in human studies.

In everyday meals, each oil can be consumed in bulk form or as a fine emulsion. In the rat, we revealed that gavage with

an emulsion of sunflower oil using soybean lecithin increased postprandial endotoxemia compared with gavage with the unemulsified sunflower oil (Fig. 5). Moreover, postprandial endotoxin accumulation was positively correlated with that of plasma triglycerides after these different products (Laugerette *et al.*, 2011). In the long term, we explored the impact of different lipid emulsifiers in the diet on metabolic inflammation. Mice were fed a high-fat diet containing 20% of lipids (mostly palm oil) or modified diets in which 1.2% of oil has been replaced with 1.2% soybean phospholipids or 1.2% milk phospholipids. The diet containing soybean PL (commonly called soybean lecithin) induced adipose tissue hypertrophy and increased markers of inflammation, including circulating LBP concentration and its expression by the adipose tissue, compared with the high fat diet devoid of PL (Lecomte *et al.*, 2016). Interestingly, milk PL did not induce such effect, which could be partly due to their effect on providing faster triglyceride digestion and absorption compared with soybean PL as also observed *in vitro* and in mice (Lecomte *et al.*, 2015). Another mechanism can be due to the differential impact of lipids on goblet cells which secrete the mucus layer in the colon (Fig. 5). Unlike soybean PL, milk PL in the high fat diet were found to increase the number of colonic goblet cells, thereby possibly contributing to an improved gut barrier that can prevent LPS translocation from the colon to the circulation (Lecomte *et al.*, 2016). Consequences in the field of infant nutrition regarding the metabolic impact of native breastmilk fat globules vs artificially formulated fat droplets would deserve to be elucidated (Bourlieu and Michalski, 2015; Gallier *et al.*, 2015).

## 6 Importance of LPS transporters and receptors regarding the inflammatory outcome of endotoxemia

LPS handled by chylomicrons during the postprandial phase would be rapidly taken up by the LBP that is the acute phase protein transporting LPS in plasma (van Dielen *et al.*, 2001). In healthy metabolic status or in obesity with low-grade inflammation, low plasma LBP concentrations are known to increase the pro-inflammatory activity of LPS (Lamping *et al.*, 1998). In fact, bacterial LPS induce a higher inflammatory response when they are bound to LBP (Mathison *et al.*, 1992; Tobias *et al.*, 1992) and are strong inducers of proinflammatory cytokine secretion (Marshall, 2005) (Fig. 1). Therefore, interest is currently growing about LBP in the context of metabolic endotoxemia studies. In our study in mice showing that a palm oil diet results in metabolic inflammation, plasma IL-6 was highly correlated with plasma LBP concentration in the palm oil group (Laugerette *et al.*, 2012). In lean to obese men, postprandial IL-6 accumulation after meals containing 10 g or 40 g fat was also correlated to plasma LBP concentration (Vors *et al.*, 2015). Moreover regarding the impact of PL emulsifiers, including soybean PL into the high fat diet resulted in higher expression of inflammatory markers in adipose tissue, namely leptin, TNF-alpha and MCP-1, together with a higher expression of LBP. In contrast, milk PL did not induce adipose tissue hypertrophy and inflammation, and both plasma LBP concentration and LBP expression in adipose tissue were lower in this group (Lecomte *et al.*, 2016).

Parallel to LBP, another endotoxin transporter is described, namely sCD14, but the transport of LPS via sCD14 would lead to a different metabolic impact. Interestingly, sCD14 was recently revealed to potentially present beneficial metabolic effects in the context of inflammation-driven insulin resistance (Fernandez-Real *et al.*, 2011). Indeed, LPS handling by sCD14 was previously reported to inhibit LPS activity by orienting them toward detoxification pathway *via* HDL (Sussman, 2002; Wurfel *et al.*, 1994), thereby exerting anti-inflammatory effects. Such mechanisms of LPS transport and inflammatory outcome were long known in the etiology of sepsis, however their implication in the context of metabolic endotoxemia and inflammation, obesity and type 2 diabetes is recent. Importantly, a dual role of sCD14 was recently revealed in humans. In non-obese humans with low sCD14 plasma concentrations, circulating sCD14 concentrations were positively associated with percent body fat, waist circumference and white blood cell count and negatively associated with insulin sensitivity, revealing a compensatory role (de Courten *et al.*, 2016). In contrast in morbidly obese participants, circulating sCD14 were positively associated with insulin sensitivity, revealing a buffering effect (de Courten *et al.*, 2016). Authors therefore speculate that, once morbid obesity develops, the capacity of maintaining sCD14 synthesis would determine the metabolic impact of endotoxemia.

Our previous mice and human studies are consistent with such proposed role of sCD14. Inflammation in mice fed a palm oil diet was highly correlated with the relative proportion of circulating transporters of LPS (Laugerette *et al.*, 2012). The LBP/sCD14 ratio was higher in this group while mice fed the

rapeseed-oil diet presented a lower LBP/sCD14, notably due to a higher sCD14 plasma concentration, resulting in a lower metabolic inflammation (Fig. 5). Therefore, our results suggest that a diet enriched with 20% refined palm oil can result in a more active and pro-inflammatory transport of LPS towards target tissues *via* a high plasma concentration of LBP and a lower concentration of sCD14. Conversely, a diet enriched with 20% rapeseed oil results in a lower inflammation both in the circulation and in the adipose tissue, notably *via* an increase of plasma sCD14 concentration (Laugerette *et al.*, 2012). Consistently in lean to overweight men overfed during 8 weeks, increased inflammatory response was associated with increased LBP/sCD14 ratio in plasma (Laugerette *et al.*, 2014) (Fig. 3).

## 7 Conclusion and future prospects

The relationship between obesogenic diets and endotoxemia is a new concept that contributes to explain the set up and development of low-grade inflammation. Several studies including ours support the concept that the digestion of a meal containing lipids increase the absorption of endotoxins naturally present in the gut, whose metabolic fate will subsequently depend on their handling by different types of transporters in plasma. The long-term consequences of postprandial endotoxemia, occurring repeatedly meal after meal, should now be more deeply elucidated, notably according to lipid composition in the diet. Of note, metabolic disorders themselves can induce and maintain inflammatory processes, which can then prevail on the amount and composition of ingested lipids. With an aim of preventive nutrition strategy, clinical data should thus be interpreted with care, and stigmatization of specific dietary fat sources should be avoided. Diets or meals tested in clinical trials are often unbalanced, notably with excessive fat amounts. Deleterious effects of lipids are then reported but such diets are also characterized by very low fiber content and high carbohydrate content. Therefore in the etiology of metabolic disorders associated with endotoxemia and inflammation, the study of postprandial phenomena should be performed using more equilibrated and realistic meals and diets. This is particularly consistent regarding lipids because they can be provided through a great variety of compositions and structures, in a wide range of food products. Our works allow to foresee that by modulating the amount, composition and/or structure of dietary lipids, notably in emulsions, nutritional strategies can be proposed to limit postprandial endotoxemia and/or to lower the metabolic impact of postprandial endotoxemia and contribute to prevent low-grade inflammation associated with metabolic diseases.

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