Multiscale structures of lipids in foods as parameters affecting fatty acid bioavailability and lipid metabolism

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[*]RMT LISTRAL: Mixed Technological Network combining academic and industrial partners, devoted to the enhancement and divulgation of knowledge regarding structured dietary lipids.

This review is respectfully dedicated to the memory of Michel Ollivon, Research Director at CNRS (Châtenay-Malabry, France), outstanding physico-chemist specialist of lipid organization, recipient of the Hilditch Memorial Lecture award, who was the initiator of the network RMT LISTRAL. We are also sadly paying tribute to Jean-Luc Vendeuvre, Food Engineer at the French Pork and Pig Institute (IFIP, Maisons-Alfort, France), outstanding expert in meat products who participated actively in RMT LISTRAL and provided unpublished data for figures in the present review, who passed away during review submission.

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Abbreviations[1]

[1] FA, fatty acid(s) ; TAG, triacylglycerol(s) ; PL, phospholipid(s); ALA, alpha-linolenic acid ; ARA, arachidonic acid ; DHA, docosahexaenoic acid ; EPA, eicosapentaenoic acid ; PUFA, polyunsaturated fatty acid(s) ; AUC, area under the curve ; BMI, body mass index.

Abstract

On a nutritional standpoint, lipids are now being studied beyond their energy content and fatty acid (FA) profiles. Dietary FA are building blocks of a huge diversity of more complex molecules such as triacylglycerols (TAG) and phospholipids (PL), themselves organised in supramolecular structures presenting different thermal behaviours. They are generally embedded in complex food matrixes. Recent reports have revealed that molecular and supramolecular structures of lipids and their liquid or solid state at the body temperature influence both the digestibility and metabolism of dietary FA. The aim of the present review is to highlight recent knowledge on the impact on FA digestion, absorption and metabolism of: (i) the intramolecular structure of TAG; (ii) the nature of the lipid molecules carrying FA; (iii) the supramolecular organization and physical state of lipids in native and formulated food products and (iv) the food matrix. Further work should be accomplished now to obtain a more reliable body of evidence and integrate these data in future dietary recommendations. Additionally, innovative lipid formulations in which the health beneficial effects of either native or recomposed structures of lipids will be taken into account can be foreseen.

Keywords: lipid, fatty acid, food, emulsion, digestion, metabolism.

Outline

1. Introduction

Dietary lipids have long been considered as energy suppliers. In the frame of preventing metabolic diseases of nutritional origin and cardiovascular risk factors such as hypertriglyceridemia, excessive lipid intake should be avoided [1, 2]. However, dietary lipids are also recognized to be essential for preserving health. For instance, the need for a balanced supply in both *n*-6 and *n*-3 polyunsaturated fatty acids (PUFA) is now supported by dietary guidelines, while various other fatty acids (FA) present specific recommended intakes [3-5]. Altogether, optimizing the bioavailability of beneficial FA while preventing the development of excessive lipemia is important for human health. However, beyond FA composition, dietary fats and oils exhibit a huge molecular and supramolecular diversity as shown **Figure 1.** Recent advances in nutrition research revealed that these various structures and the physical (liquid *vs* solid) states of lipids in food products can modulate FA release and bioavailability during digestion and their final metabolic fate. The location of FA on a triacylglycerol (TAG) or on a phospholipid (PL), their position on the glycerol backbone, the supramolecular arrangements of lipid molecules for instance in the form of emulsion droplets that vary according to their sizes, interfacial composition, and the amount of fat in crystallized state may impact on their digestibility and metabolism. This could modify their health impact.

The present review is focused on the recent available evidence showing that the structures of dietary fats and oils, viewed from the molecular to the food matrix scales can modulate FA bioavailability and lipid metabolism.

2. Intramolecular structure of triacylglycerols and fatty acid metabolism

The intramolecular structure of TAG corresponds to the position, or so-called regiodistribution, of the FA chains on the glycerol backbone (internal *sn*-2 position, external *sn*-1 and *sn*-3 positions; **Figure 1A**). It has long been suspected to influence FA bioavailability and metabolism and thus, the nutritional impact of TAG. Several reviews on this topic highlighted conflicting results [6-15]. The different models used, the studied molecular species of TAG and their purity, the presence of other non-lipid components may explain this apparent inconsistency. However, most studies also indicate that the position of the acyl groups on TAG affects their hydrolysis and subsequent FA absorption, which can modify some cardiovascular risk factors [16]. We will first summarize the identified mechanisms; then the data obtained *in vitro*, in animal models or in humans either with natural lipid sources or with restructured TAG are more deeply reviewed.

2.1 The mechanisms linking FA bioavailability to TAG intramolecular structure

FA can be absorbed only when released from the TAG structures as non-esterified FA (free FA = FFA) or as 2-monoacylglycerols (2-MAG) after digestive lipolysis (**Figure 2**). Accordingly, in animals and human infants, *sn*-2 esterified FA are efficiently absorbed as 2-MAG [17-19]. In this way they can be directly used by enterocytes for the synthesis of TAG participating to chylomicron assembly [20]. Consequently in infants, during the postprandial phase, FA located on the *sn*-2 position in dietary TAG will mainly keep this location in chylomicron-TAG. Also in adults, after consumption of fish oil, DHA incorporates faster than EPA in plasma TAG, certainly because DHA was mostly on *sn*-2 and EPA on *sn*-1,3 positions [21].

It should also be underlined that digestive lipases hydrolyse more specifically FA esterified on *sn*-1,3 positions of glycerol backbone as compared with the *sn*-2 position [22]. Pancreatic lipase

exhibits low hydrolytic activity when TAG contains long-chain polyunsaturated fatty acids (PUFA) with double bonds close to the carboxyl group [23-25] because of their steric hindrance, especially when they are located in *sn*-1 or *sn*-3 position [26-29].

Therefore, restrained TAG lipolysis, resulting from the intrinsic regiospecificities of lipases or of their limited access to the substrates, may result in different kinetics of release of absorbable FA according to lipid sources. This may impact the metabolism of TAG-rich lipoproteins. Additionnally, when long-chain saturated FA esterified on *sn*-1 & *sn*-3 positions are released by digestive lipases, they tend to form complexes with calcium or magnesium ions, constituting FA soaps. The latter can be further lost in stools instead of being solubilized in mixed bile salt micelles or vesicles absorbable by enterocytes. However, this would be specifically relevant to infant nutrition; in human adults, stearic (18:0) and palmitic (16:0) acids are well digested and absorbed regardless of their *sn*-position in TAG [30-32].

Lipoprotein lipase (LPL) responsible for hydrolysis of circulating TAG is also specific for the FA esterified at the external position of TAG. Accordingly, in rats, 16:0 and 18:0 on *sn*-2 position of circulating TAG slowed down chylomicron clearance and prolonged postprandial lipemia [33, 34]. In humans, chylomicrons remain in contact with LPL long enough to be efficiently hydrolyzed, all the more than the local environment allows 2-MAG to be isomerized into 1(3)-MAG whose FA are efficiently released [35, 36]. Consistently, when healthy young male adults consumed randomized lipids in which 30 % of 18:0 was on *sn*-2 position, the proportion of 18:0 on *sn*-2 in resulting chylomicron-TAG in the postprandial phase remained constant at ~22% [37].

2.2 Bioavailability of fatty acids in differently structured natural dietary triacylglycerols

Different natural fats or oils contain basically the same major FA that are differently distributed within the glycerol backbone (**Table 1)**. For example, palmitic acid is preferentially located on the *sn*-2 position in milk fat and lard while it is concentrated on the *sn*-1,3 positions in beef tallow, soybean oil and cocoa butter. Unsaturated FA (oleic, linoleic…) are mainly located on *sn*-2 position in soybean oil and cocoa butter while in lard, oleic acid is mostly on external positions [11].

The intestinal absorption (postprandial kinetics of FA in the lymph) of fats and oils presenting various FA profiles, TAG structures and liquid *vs* solid states were compared in the rat [38]. The percentage of FA absorption at 8h and 24h after administration of cocoa butter and palm oil containing saturated FA on *sn*-1,3 was lower than from lard with saturated FA on *sn*-2 position.

In the newborn, 16:0 esterified to the *sn*-2 position of human milk TAG is absorbed intact and re-esterified to TAG for secretion into plasma. This preferential esterification of 16:0 in human milk partly explains the high absorption rate of human milk fat [39, 40]. In contrast, 16:0 would be absorbed predominantly as a non-esterified FA from conventional infant formula where palmitic acid is mostly on *sn*-1, 3 positions [41].

ALA provided by rapeseed oil alone, with 56% in the *sn*-2 position, or in oil blends (58% on *sn*-2) was mainly maintained in this position in lymphatic chylomicrons (40% and 44% on *sn*-2, respectively) [42]. Conversely to fish oil, oils from marine mammals such as whales or seals are composed of TAG with PUFA located mainly on *sn*-1,3 positions [43]. DHA and EPA from whale oil are less easily released by pancreatic lipases *in vitro* than other FA (mainly 16:0 and 18:1) [23]. Accordingly, *in vitro* colipase-dependent pancreatic lipase, bile salt-stimulated lipase (BSSL) and both enzymes hydrolysed 18:1 more efficiently than DHA esters, with accumulation

of DHA in MAG or diacylglycerols (DAG) with BSSL and colipase-dependent lipase respectively [44]. This could be due to steric constraints due to the double bond located close to the carboxyl group independently from FA location on TAG, because DPA (22:5 *n*-3) on external positions did not present such a resistance to lipolysis [23, 25]. Postprandial kinetics of EPA and DHA in the rat lymph after an intragastric administration of fish oil or seal oil [27] showed that *n*-3 PUFA were better absorbed from fish oil during the first hours of digestion; however, regarding total assimilation after 24h, the effect did not remain significant. After seal oil administration, a significantly higher load of *n*-3 PUFA was esterified in the *sn*-l,3 positions of chylomicron TAG compared with fish oil [28].

2.3 Studies involving synthetic or interesterified triacylglycerols

The position of the acyl groups on TAG molecules can be modified using interesterification. This process uses chemical or enzymatic catalytic reactions (i) to incorporate specific FA in TAG or (ii) to obtain a random distribution of the FA naturally present in the TAG on the different *sn*-positions of the glycerol backbone (so-called randomization). While their FA profile is overall unchanged, the melting temperature of the randomized oils can be modified [45, 46]. Therefore, randomization offers an alternative to hydrogenation to produce tailored fats with improved mechanical properties. Food industry also uses interesterification to produce functional ingredients such as Betapol^{TM}, used in some infant formula to simulate breastmilk TAG with a high amount of 16:0 on *sn*-2 [47 , 48].

2.3.1. In vitro and animal studies

Several studies have used synthetic TAG obtained by interesterification of natural fats and/or pure TAG. Interesterification results in TAG with reasonably well-controlled intramolecular

structures while not reflecting the complexity and diversity of structures observed in natural fats. The *in vitro* hydrolysis rate by pancreatic lipases is 2-3 fold higher for TAG with long-chain FA on *sn*-2 and medium-chain FA on *sn*-1,3 (MLM) than for TAG carrying medium-chain FA on *sn*-2 and long-chain FA on *sn*-1,3(LML) [49]. Moreover, plasma TAG was greater in the rat after 4 weeks of MLM consumption compared with LML [49]. These results and previous studies [50, 51] show that FA are better absorbed when long-chain FA are on the *sn*-2 position and medium-chain FA on external *sn*-1,3 positions.

In rats, long-chain FA such as 18:1/16:0/18:1 (OPO) was better absorbed and transported than 18:1/18:1/16:0 (OOP) [52]. The absorption of synthetic TAG containing only 18:0 (S) and 18:1 (O) was also studied [53]: OSO, SOO, SOS & OSS, together with or without calcium and magnesium ions. Oleic acid was efficiently absorbed (>93%) regardless of TAG structure while the percentage of absorption of 18:0, with and without divalent cations respectively, was 98% & 99% for OSO, 55% & 96% for SOO, 37% & 70% for SOS and 59% & 60% for OSS [53]. Most recently, similar results were obtained with rats fed (SOS), resulting in lower absorption compared with (OSS); importantly however, statistical significance was only reached at the highest dietary calcium concentration [54]. In the presence of divalent ions, 18:0 is poorly absorbed when esterified on the external positions of TAG. Thus the impact of TAG structure on FA absorption is associated with the presence of such Ca^{2+} and Mg^{2+} ions in the diet. At alkaline pH insoluble FA soaps are produced from the ionised saturated FA released from lipolysis. In contrast, the FA are efficiently absorbed as 2-MAG when esterified on *sn*-2. One may notice that the melting temperature of the TAG and DAG formed by the first hydrolysis can also influence the absorption of 18:0. For example, 1,2-distearin issued from OSS presents a melting temperature of 60°C, well above body temperature, that may lower lipase activity [53, 55].

Similar studies have been performed in animals with TAG containing PUFA or CLA. In the rat, rumenic acid (CLA 9*cis*, 11*trans*; major isomer in milk fat) was better absorbed and more β-oxidized when located on *sn*-1,3 positions as in milk fat, compared to *sn*-2 position [56]. A

significantly higher lymphatic transport of PUFA was also observed during postprandial kinetics with a structured oil containing mostly PUFA on *sn*-2 and 10:0 on *sn*-1,3 (maximum obtained at 3 h with ~65 µg/min and 75 µg/min for DHA and EPA respectively) *vs* a randomized oil where PUFA were more randomly located on the 3 positions (35 µg/min maximum for either DHA or EPA obtained at 5 h) [57]. However, cumulative amounts after 24 h were not significantly different for both oils [57].

Conversely, using similar oils but with different PUFA proportions, the lymphatic transport of PUFA and cumulative absorbed amounts after 24 h were slightly higher using a randomized oil [29]. However, lymphatic absorption of PUFA was similar using two types of structured TAG with similar compositions (40% of 10:0 and 40% of PUFA) but with PUFA located mainly on *sn*-2 (MLM) or on *sn*-1,3 (LML) [26]. In turn, native fish oil that contained less PUFA (28%) but more 16:0, 18:1 & 20:1 resulted in higher PUFA absorption than using structured TAG in the first 8 h of digestion, longer overall absorption being similar among the three lipid sources [26]. The metabolic fate of ALA was also studied in rat, with TAG structured so that ALA was strictly grafted in the internal or external position (O/ALA/O vs ALA/ O/O) [58]. The lymphatic absorption of ALA was similar regardless of its location on the glycerol backbone. Noticeably, the initial internal position of ALA was relatively maintained at the peak of lipid absorption (46±2%, 4 hours after intragastric intubation of structured TAG). This may result from the presence of a MAG lipase at the enterocyte level, as previously suggested [57]. Both *in vitro* and *in vivo* experiments showed faster hydrolysis and FA transport when fish oil was the substrate *vs* structured TAG. However, total FA amounts recovered after 24 h were similar[26]. This suggests that in physiological conditions, with long digestion time and enzyme excess, differently structured TAG result in similar bioavailability of FA.

Other studies showed that an increase in the proportion of palmitic acid in *sn*-2 position by interesterification of TAG in coconut oil and palm olein improved its absorption in the rat, estimated by amounts of saturated FA in feces after several days of controlled diet [59]. Similarly

in rat, effects on metabolism of palm oil and lard either native or interesterified were found after several months of controlled diet [60]. Lower plasma TAG was observed with lard interesterification (decrease in the 16:0 proportion in s*n*-2) and greater platelet aggregability with palm oil interesterification (increase in 16:0 proportion in s*n*-2). Authors concluded that the FA in the *sn*-2 position influence to the greatest extent the physiological effects [60]. In piglets, absorption of 16:0 from dairy formula estimated by 16:0 in plasma TAG was higher when located on *sn*-2 [61, 62]. However, rats fed during 24 days with diets enriched in fish oil or nut oil either native or randomized did not exhibit any difference in apparent lipid absorption estimated by steatorrhea [63, 64]. Randomization did not modify neither plasma cholesterol and TAG concentrations, nor the fasting FA profile of plasma lipids after the diet [63, 64].

In rabbits, interesterification of fats and oils did not change plasma lipid and lipoprotein concentrations; however, increasing the proportion of palmitic acid on *sn*-2 compared to *sn*-1,3 resulted in increased TAG atherogenicity. Native lard with 16:0 mainly on *sn*-2 may be more atherogenic than interesterified lard [65] while native palm oil and cottonseed oil (with 16:0 mainly on *sn*-1,3) may be less atherogenic than their interesterified counterparts [66, 67]. These effects would be due to a better absorption and *in vivo* residence of palmitic acid in blood when esterified on *sn*-2 [33, 68]. However, the opposite had previously been observed when rabbits were fed native nut oil (with saturated FA on external positions) that turned out to be more atherogenic that the interesterified nut oil [69].

2.3.2. Human studies

Several studies have been performed in newborns or human adults. Authors have either measured postprandial lipemic response to a single meal or compared the impact of different lipid sources consumed during several weeks on cardiovascular risk factors. Results were less clearcut than in animal models and sometimes conflicting [11 , 70].

When newborns consume synthesized TAG formula (39% of 16:0 in *sn*-2 position) compared with standard infant formula (6% of 16:0 in *sn*-2 position) or human milk (81% of 16:0 in *sn*-2 position), lipid and lipoprotein metabolism may be affected. Amounts of 16:0 in the *sn*-2 position of plasma chylomicron TAG was higher in breast-fed infants or in infants fed synthesized formula with predominantly 16:0 at *sn*-2 position. [71]. In infants, the absorption of 16: 0 is more efficient when it is on the *sn*-2 position: 8-fold less loss in stools using infant formula with lard TAG where the native 16:0 is in the *sn*-2 *vs.* randomized lard [72].

Conversely, in human adults, incorporation of 16:0 in chylomicron TAG was similar 6 h after consuming native palm oil (with 16:0 mainly on *sn*-1,3 and 18:1 mainly on *sn*-2) or interesterified palm oil, while palm oil interesterification slightly reduced postprandial lipemia (AUC of plasma TAG) [73]. A trend was also observed with native and randomized lard [74]. In contrast, similar concentrations of plasma TAG were measured 6 h after consumption of 16:0-rich fats with various TAG intramolecular structures [75] or with differently structured TAG containing saturated FA (16:0 or 18:0) and 18:1 [35, 36]. A greater postprandial lipemia (AUC of plasma TAG up to 6 h post-meal) was obtained with native *vs* randomized dietary palm oil [76]. However, FA composition of TAG in chylomicrons was not significantly changed. The same trend was observed for native *vs* randomized shea butter [77]. These results were explained by the presence of a higher proportion of fat being solid at 37°C after randomization than in the native fats (the metabolic effects of fat thermal properties will be reviewed in section 2.4). Accordingly, native cocoa butter (rich in POS and SOS) induced a greater incorporation of 16:0, 18:0 and 18:1 in plasma lipid and a higher postprandial lipemia (AUC of plasma TAG during 6 h of digestion) than interesterified cocoa butter [46].

Clinical trials in adult humans also aimed to measure the impact of intramolecular TAG structure on some cardiovascular risk factors after several weeks of controlled diets. Lean subjects consuming for 3 weeks 30 g/day of native *vs* randomized shea butter exhibited similar fasting plasma concentrations of LDL- and HDL-cholesterol [77]. Several studies confirmed these data

and showed that either in lean or hypercholesterolemic subjects, 3 or 4 weeks of controlled diets with various types of structured fats did not impact blood lipids. The different studies compared native palm oil *vs.* interesterified palm oil rich margarines [83, 84] or native *vs*. interesterified vegetable oils [85] or native *vs.* interesterified butter [86]. Beside blood lipids markers, also no difference was found in other parameters such as such as PAI-1, F-VIIa and fibrinogen [85].

Altogether, these clinical trials strongly suggest that for human adults, consumption of interesterified fats and oils during several weeks does not impact plasma lipid concentrations compared with native fats and oils.

Interestingly, above-mentioned studies show that TAG intramolecular structure may influence lipid digestion and absorption and may affect some metabolic outcomes. This has been mainly observed *in vitro,* in animals and in human newborns while studies conducted in human adults do not confirm these results. Different mechanisms have been identified. As discussed before, *in vitro* and *in vivo* studies indicate that FA, more particularly long-chain saturated FA, are better absorbed when located preferentially on *sn*-2 compared with other fat and oil sources where these FA are located on external *sn*-1,3 positions.

In human adults, lipid absorption appears to be more closely correlated with the percentage of solid fat at body temperature. Indeed, when FA reorganization on TAG molecule modifies their thermal properties by producing asymmetric TAG (e.g., SSO) or trisaturated TAG that are still crystallized at 37°C, then a lower postprandial lipemia is observed (see section 2.4). Deeper studies are now necessary to better identify the relative impact of fat thermal properties *vs* proportion of saturated FA on *sn*-2. Despite all these results highlighting the importance of TAG intramolecular structure on lipid bioavailability, up to date, clinical studies in lean humans suggest that consumption of structured TAG does not impact cardiovascular risk factors compared with native TAG. Still, studies remain to be performed in subjects suffering from features of the metabolic syndrome and for longer dietary intervention periods [11].

2.4 The intramolecular structure of triacylglycerols can affect FA digestion and metabolism through its influence on the liquid or solid state of fat

2.4.1 The physicochemical properties of fats

FA melting temperature depends on their carbon chain length and unsaturation (number and position of the double bond). Long-chain saturated FA have high melting temperature, above 40°C. The position of FA on TAG molecules and the polymorphism (ability of TAG to organise as various forms) also affect the melting temperature of TAG. Because natural oils and fats are complex mixtures of TAG, they do not have a single melting point such as pure compounds, but melting and crystallisation ranges. For example, cocoa butter has a melting temperature range from 25 to 35°C, whereas milk fat has a melting range from -40 to 40°C.

TAG mixtures rich in unsaturated FA are liquid at room temperature (olive oil, fish oil) while saturated FA rich mixtures may have a solid fat phase at room temperatures (cocoa butter, palm oil, milk fat). Some dietary lipids are mixtures of TAG in the liquid state and TAG that remain in the solid state (crystals) at their temperature of consumption (for example milk fat). The solid fat content at a fixed temperature mainly depends on the TAG composition, temperature and the thermal history (kinetic of cooling, duration of storage). Fat crystals can be characterised at a microscopic level (shape and size of fat crystals, orientation in lipid droplets) and at a molecular level (organisation of TAG in lamellar structures of various thicknesses, and corresponding to various polymorphic forms). The complexity of TAG polymorphism and the impact of crystal characteristics on fat functional properties have been widely studied [78-88].

2.4.2 Thermal profile and polymorphism of natural fats and oils

Figure 3 presents the thermal properties and melting temperature of various fats and oils. The crystallisation properties of milk fat in the anhydrous state and in milk fat globules have been

widely studied [89, 90], as well as in milk fat fractions (stearins and oleins) [91]. The size of fat crystals, their location within milk fat globules but also the types of crystals that are formed at a molecular level mainly depend on the cooling rate and the time of storage at low temperature (4 to 7°C) [89, 92].The types of crystals also depend on the dispersion of TAG in emulsion droplets. Several types of crystals coexist within milk fat globules [93-96]. Milk fat is partially crystallised in dairy products at the temperature of their consumption, while in butter the melting profile depends on the FA composition of milk fat [96]. Milk fat is also partially crystallised in whipped cream and in ice-cream. In cheeses, milk fat is partially crystallised at T < 41°C: about 3% of milk fat remains solid at the temperature of ingestion 37°C and more that 50% of milk fat is solid at 4°C [97, 98]. In other animal products such as pork, beef and sheep, dietary lipids are partially solid with beef tallow melting at 40 to 50°C and lard in the range 36-42°C. Due to its FA composition including large proportions of oleic acid and presence of PUFA, lard exhibits a wide melting range: the formation of 4 polymorphic forms have been reported in lard, with a melting profile spanning from -30 to 50°C [99]. Different melting profiles were observed according to actual FA composition of the sample and between (i) retroperitoneal lard *vs* dorsal subcutaneous lard, and (ii) native lard *vs* pure fat extracted from lard and used to manufacture pâté [100, 101]. For instance, the melting point of lard made by slow cooling was found to be 45°C and reached 48.7 °C when used as an ingredient in liver pâté, the total fat previously solvent extracted from the lard exhibiting a melting point of 39 °C [101]. **Figure 3B** shows that solid fat content in pork rillettes *vs* pork lard and duck fat *vs* duck potted meat vary according to major TAG species present in the fat.

Regarding vegetable fat, the crystallisation properties of palm oil and palm oil fractions (stearins and oleins) have been studied [102 , 103, 104]. At room temperature, palm oil is partially solid. The crystallisation properties of cocoa butter have been more widely studied because they are important for the quality of chocolate. The polymorphism of cocoa butter corresponds to 6 polymorphic forms noted I to VI in their increasing order of melting temperature [105 , 106].

Cocoa butter melts in the mouth at 37°C, therefore it can be in liquid form during gastric digestion.

Therefore, the presence of TAG crystals at body temperature raises the question of the digestion of high-melting point TAG that are solid in dairy products, meat products and foods manufactured with partially solid vegetable oils.

2.4.3 Studies showing that TAG thermal properties may modify digestion, absorption and lipid metabolism

The presence of a solid fat phase has an effect on the digestion, absorption and metabolism of dietary lipids. The solid fat phase limits the enzymatic hydrolysis of TAG and then their absorption: this phenomenon was observed in dogs, rats and rabbits and discussed for a long time [107-111]. Therefore mixtures of TAG with the same FA composition but different intramolecular structures with different melting temperatures, crystallization properties [112, 113] and percentage of lipids in the solid state at body temperature (so-called solid fat content or SFC, at 37°C) may present different rates of hydrolysis and consequently different FA absorption kinetics and bioavailability [6, 77].

Very recently, the level of *in vitro* hydrolysis by pancreatic lipases of an emulsion prepared with tripalmitin in the solid state was shown to be lower than the same emulsion with TAG in the liquid state [114]. In humans, the high melting temperature (>37°C) of TAG rich in palmitic or stearic acids is responsible for the low absorption of these FA [6, 7]. The postprandial kinetics of plasma TAG is higher after consumption of sunflower oil (0% of solid lipids at 37°C) compared to shea butter rich in 18:0 (22% solid lipids at 37°C).

Solid *vs* liquid state and also different percentages in solid TAG at 37°C between oils and native or randomised fats affect postprandial lipemia [76, 77, 115, 116]. These recent results in humans confirm previously reviewed animal studies [55]. Among these former studies, the digestion and absorption of natural and modified fats in the rat are reported to be correlated with their melting

temperature, with an important decrease in absorption for melting temperatures over 50°C [117]. In the rat, tristearin (tri-18:0; melting temperature = 73°C) is less digested and absorbed than triolein (tri-18:1) which is totally liquid at 37°C [118]. Lipid absorption (area under the curve of plasma TAG during 3 hours after feeding) is also lower in guinea pig fed the high melting temperature fraction of milk fat (42-44°C) compared to the animals fed the low melting temperature fraction (13-14°C) of milk fat [119], consistent with results in rats regarding different lipemia in lymph and plasma after feeding such fats [120, 121].

After interesterification, cocoa butter contains a larger proportion of TAG containing 3 saturated acyl groups (PPP, PPS, SSP and SSS). Such TAG have a high melting temperature and thus a higher percentage of solid fat at 37°C in interesterified cocoa butter (37% *vs* 1% in native cocoa butter), which resulted in lower postprandial lipemia in humans [46]. In obese humans, but not in non-obese, a mixture of oleic sunflower oil and fully hydrogenated canola oil (70:30) rich in OOO and SSS (containing 19% of solid fat at 37°C) induced a lower postprandial lipemia (AUC of plasma TAG during 6 h) than the same oil mixture previously randomized and thus containing only 6% of solid fat at 37°C, with increased proportion of SOS and OOS and strongly decreased proportion of SSS [116]. These results confirm those obtained in the rat [122].

We hypothesize that the physical state of lipids may affect the ability of lipases to access and hydrolyze TAG. The influence of the physical state of animal fats and particularly the proportion of solid fat on lipid absorption remains poorly documented. Further research would thus be needed to explore the advantage of optimizing the physical state of fat to control postprandial lipemia in the context of metabolic diseases.

3. Molecular level: fatty acids bound to different lipid classes are metabolized differently

Dietary FA mainly exist as esterified in TAG (97% of dietary lipids) but also in PL (3%). Diacylglycerol-rich oils (so-called DAG-oils) are also available while specific bioactive FA may exist under free or ethyl ester forms in specific dietary supplements. FA are released differently by digestive enzymes (lipases, phospholipases) depending on the type of molecules they are esterified on [17, 123]. Many studies have been performed to identify the impact of the carrier molecule on FA bioavailability [12, 124]. Previous reviews dealt with the digestion of TAG [125, 126], here we review studies comparing the digestion of TAG *vs* other lipid molecules in food products.

3.1 Absorption and metabolism of fatty acids in phospholipids *vs* triacylglycerols

In the rat, incorporation of *n*-3 FA in plasma and liver lipids was more efficient when it was fed with liposomes of marine PL compared to TAG oil [127, 128]. However, the hypotriglyceridemic effect of *n*-3 FA after 2 weeks of feeding was similar regardless of the PL or TAG form [128]. Feeding rats with marine lipids containing EPA and DHA in the form of either PL (in liposomes) or TAG (in oil) induces different effects on liver lipid metabolism. After 3 days of treatment, PL *vs* TAG feeding induced higher liver PL but poorer in EPA, higher expression and activity of CPT-I, and up-regulation of intracellular proteins involved in free FA uptake and lipid synthesis, probably leading to a greater β-oxidation of EPA [129]. However, the relative impact of carrier molecule (PL *vs* TAG) and of the dispersion state (liposome *vs* oil) remains unclear. Similar results have been obtained with linoleic acid in mice [130] and with ARA in baboon neonates [131] . A slight increase of steatorrhea (lower lipid absorption) was observed in rats after 3 weeks

of feeding a diet enriched in egg TAG-PUFA compared to a diet enriched in egg PL-PUFA [132]. In piglets fed these two dietary PUFA sources, the percentage of ARA and DHA increased in the PL of HDL, while they decreased in LDL, when these PUFA were fed as PL. However, plasma TAG and total cholesterol were similar in both diets [133]. Recently, PL and TAG containing long-chain *n*-3 PUFA were found to be equally efficient in lowering metabolic inflammation when added in a high fat diet in mice, while PL had a major effect on decreasing adipocyte size that was not observed using TAG [134]. Altogether, these results may partly explain differences observed between PL-rich krill oil and TAG-rich fish oil in clinical trials in humans [135-137]. For instance, krill oil consumed daily for 3 months was more effective than fish oil for the reduction of glucose, TAG and LDL levels in hypercholesterolemic patients [137], although no adjustment for confounding factors had been made [136].

Interestingly, opposite results were obtained in piglets fed DHA for 16 days as TAG from unicellular algae oil, which induced higher total DHA concentration in plasma than as egg PL, despite similar FA profiles [138]. Both in the rat and in elderly humans, dietary supplementation with DHA-rich egg PL induced increased DHA and ARA accretion in plasma and erythrocyte membranes, while a depletion in ARA was observed for supplementation with DHA in TAG of fish oil [139, 140]. Finally, conflicting results have been obtained in newborns regarding DHA bioavailability from formulae enriched in PL-DHA *vs* TAG-DHA [141, 142].

Recent reviews reported potential nutritional benefits of dietary PL-rich ingredients from milk fat globules membrane (MFGM) such as hypocholesterolemic and anticarcinogenic activities [16, 143-146]. Research in this field now greatly expands [147]. In mice, adding a PL-rich milk extract in a fat-rich diet induced a decrease of plasma and liver lipids [148, 149]. In humans, PL-rich milk fractions might reduce postprandial lipemia after milk fat consumption [150]. However, plasma lipids of healthy volunteers supplemented MFGM or egg PL for 4-weeks were similar while a tendency towards a lower cholesterolemia was observed with dairy PL [151], which led authors to conclude that further studies should be performed in dyslipidemic subjects.

Nutraceutical applications of PL of the MFGM have been discussed [143, 152-154]. However, we cannot rule out that other components of the MFGM, including minerals and specific proteins and enzymes such as xanthine oxidase and butyrophilin, may partly account for the observed results [16].

3.2 Other lipid classes: diacylglycerols, esters, lysophospholipids

DAG-rich oils can be obtained from vegetable oils through controlled hydrolysis. These new oils are considered as GRAS (« *Generally Recognized As Safe »)* in the US and can thus be used in human diet [155]. Several studies in animals and humans showed that 1,3-DAG present an hypotriglyceridemic effect and reduce postprandial lipemia compared with TAG with a similar FA composition [156-159]. However, DAG-DHA and TAG-DHA would have similar effects on lowering triglyceridemia in the rat [160]. Altogether, these studies suggested that DAG-oil consumption may have beneficial effects on lipid metabolism [160-162].

Ethyl esters of EPA and DHA had similar incorporation rates than TAG in plasma lipids in humans after 14 days [163], consistent with other data [164]. However, they exhibited a lower hydrolysis rate by pancreatic lipases than TAG [163]. Absorption of EPA and DHA in humans, estimated by FA incorporation in plasma TAG after a single bolus, was also lower after ethyl esters than TAG intake [24] ; the highest bioavailability being obtained with FFA, which contradicts data obtained in rats with marine free FA [64]. Conversely, ethyl esters were more efficient to increase the amount of EPA in plasma PL and cholesterol esters in the rat, than TAG or PL [165]. Experimental designs can explain discrepancies: the kinetics of EPA and DHA absorption, rather than the total amount of FA in plasma several hours after consumption, were influenced by the carrier form, [166, 167].

Finally, lysophosphatidylcholine (LysoPC) was also found to be an efficient carrier of long-chain PUFA to the brain [168, 169]. This unique property has been valued by designing a structured

lysolecithin containing one DHA on *sn*-2 position and a functional group in *sn*-1, thus ensuring structure stability and efficiency of LysoPC as a carrier molecule for PUFA [170].

4. Supramolecular level: the organization of lipids in food products can modulate their metabolism

TAG, the main dietary lipids, can be consumed as visible or as hidden fats. Visible fats are non-emulsified lipids such as oils, adipose tissues, or water-in-oil emulsions such as butter and spreads. Hidden fats are dispersed in the form of droplets of sub-millimeter sizes surrounded by a liquid or semi-liquid, aqueous phase (oil-in-water emulsions) or inserted in a solid phase (encapsulated lipids) [171, 172]. In oil-in-water emulsions the TAG phase is stabilised by surface-active molecules, namely polar lipids, surfactants or proteins, so-called food-grade emulsifiers.

In raw foods, dietary PL and more generally polar lipids are also present in cell membranes (e.g. meat, fish) or at the TAG/water interface of natural assemblies such as oleosomes, lipoproteins of egg yolk and milk fat globules. In processed foods, lecithins of vegetable origin (e.g. soya, rapeseed, sunflower) or animal origin (e.g. egg yolk), and MAG and DAG, possibly after additional treatments (fractionation, hydrolysis, hydrogenation) are widely used in the food industry as stabilizing agents and as emulsifiers. Lecithins from brain, krill or MFGM are other potential sources of lecithins. Indeed the composition in fatty acid and polar lipid classes of these lecithins varies in large proportions according to their origin and the production process. These polar lipids adsorb at the surface of the TAG droplets, making them less sensitive to destabilisation phenomena [173]. They are also able to interact with othe components of the food matrix shuch as proteins and polysaccharides (i.e. starch). Additionally, amphiphilic lipids such as phospho- and glycolipids, sphingolipids, MAG and DAG and non-esterified FA, organize in

various lipid structures such as micelles, vesicles, liposomes, etc when dispersed in an aqueous medium [174-176]. Liposomes of PL are used for vectorisation of therapeutic molecules for oral and parenteral applications [177, 178].

4.1 Native and recomposed supramolecular structures of lipids in raw and processed foods

4.1.1. Organization of milk lipids

The organisation of milk lipids has been widely studied in milk and various dairy products for the last 10 years. Many dairy products are oil-in-water emulsions in which TAG are dispersed in an aqueous liquid phase (milk, cream), in a partially gelled phase (yoghurt, cheeses) or in a dry medium rich in proteins (powders). In milk, the size distribution of the milk fat globules ranges from 0.1 to about 15 µm, with a mean diameter around 4 µm [179-181]. Fractions of milk fat globules with various sizes can be obtained from the native milk with processes such as centrifugation [182] and, more selectively, with cross-flow microfiltration [181]. The milk fat globules are covered by MFGM, a biological membrane, composed by three layers of polar lipids embedding cholesterol, proteins, glycoproteins, enzymes, vitamins and other minor components [183]. In this membrane, sphingomyelin laterally segregates in liquid-ordered domains surrounded by a matrix of glycerophospholipids (PE, PC, PI, PS) in the liquid-disordered phase [146, 184, 185].

During milk processing the structure of milk fat globules is highly altered by mechanical and thermal treatments [186], but also by biochemical (enzymatic) changes as reviewed in [187]. Raw milk is first cooled, then generally partially or totally skimmed, homogenised and then pasteurised or sterilised. Homogenisation of milk induces a huge decrease in the size of milk fat globules from 4 to 0.5 µm or less, depending on the pressure applied (from 50×10^6 to 300×10^6

Pa) [186]. It therefore induces an increase in the surface area of the fat globules. As the excess of water/milk fat interface cannot be covered by the MFGM components, it gets covered by other surface-active molecules present in milk, namely casein micelles and whey proteins. Additionally, some fragments of the MFGM can be scraped from the interface and form vesicles in the aqueous phase, while the smallest milk fat globules may not be affected by homogenisation [83, 188]. During the thermal treatment of milk, whey proteins also interact and aggregate with the MFGM proteins and with the casein micelles adsorbed at the surface of fat globules [189].

Confocal microscopy reveals *in-situ* the organisation of lipids in milk and dairy products [184, 190]. In cheeses, milk fat is either (i) dispersed as native milk fat globules (soft cheeses), (ii) present as fat globules more or less aggregated or coalesced with reorganisations in the MFGM, (iii) dispersed as small fat globules covered by proteins after high shear stress homogenisation (blue cheeses, some fresh cheeses), or iv) in the form of free fat domains covered by milk polar lipids (hard-type cheeses) [96, 98, 191, 192]. In dairy powders, lipids are dispersed as droplets or present as free fat [193, 194]. In butter, partially crystallised TAG forms the continuous phase, in which water droplets are dispersed, forming a water-in-oil emulsion [195]. In whipped creams and ice-cream, TAG are present at the gas/water interface and participate in foam stabilisation [88].

4.1.2. Organization of lipids in meat and meat products

In meat, TAG are mainly present in the adipocytes, that form the adipose tissue. TAG can also be found in the muscles in the form of isolated adipocytes or droplets and within cell muscles. PL that represent around 0.5 to 1 g/100g muscle are mainly located in cell membranes. They are a significant source of dietary PUFA, including *n*-3 long-chain PUFA provided the animals were fed n-3 enriched diets [196-200]). When adipose tissue is not consumed, raw meat does not contain more than 6 g total lipids /100 g, around half of them being composed of unsaturated FA.

Therefore, according to SU.VI.Max survey, meat and meat products represent for French adults around 21 % and 50 % of linoleic and arachidonic dietary supplies and 8 and 17 % for DHA and EPA supplies [201]. Noteworthy, the most unsaturated FA are located in *sn-2* position of the glycerol backbone in these food products. Apart from ham, most of processed meat products contain high amounts of lipids mainly as TAG and revealed to be significant sources of saturated FA. In lard and tallow TAG are in the form of free fat. In processed meats, fat inclusions of µm to mm size are more or less protected by the gelled protein matrix, making possible the presence of free fat domains and even some remnant adipocytes [202-206]. These fats are partly crystallised at ambient temperature, and sometimes even at body temperature, due to the presence of more than 40% of long-chain saturated FA, palmitic acid being mainly located in *sn-2* position in lard [100].

Most of muscle foods are consumed after a cooking step, which can affect the nutritional properties of the lipids. Indeed, muscle foods contain both long-chain PUFA and heme iron provided in its majority by the heme protein, myoglobin. The thermal treatment therefore favors lipid oxidation [207]. The reaction leads to formation of oxidation products such as volatile compounds involved both in the desirable cooked meat flavor and in undesirable off-flavors [208] and in deleterious oxidation products such as cytotoxic aldehydes that lead to protein carbonylation [209], which can be involved in colon cancer development [210], and possibly to loss of PUFA and vitamins. Freezing is also currently applied to increase the lifetime of meat, meat products and fish. However, both lipolysis and oxidation may occur at the frozen state, depending of the initial freezing conditions, temperature and duration of frozen storage [211].

4.1.3. Organization of lipids in egg yolk

Lipids represent about two-thirds of the dry matter of egg yolk, or nearly 6 grams of fat per egg. These lipids consist mainly of TAG (65%) and PL (29%) [212]. In egg yolk, lipids are dispersed

in the form of lipoproteins, e.g. high density (HDL) and low density (LDL) lipoproteins. HDL have a size ranging from 0.2 and 2 µm, with large variation depending of physico-chemical conditions, whereas LDL have a size ranging from 17 and 60 nm with a mean diameter of 30 nm. Lipoproteins from egg yolk are constituted by a hydrophobic core rich in TAG and cholesterol esters which is covered by a monolayer of PL and apoproteins. Using centrifugation, it is possible to separate the plasma (upper layer) that contains the LDL, from the granules (pellet) that contains the HDL [213]. The composition, structure and properties of the HDL and LDL have been characterised [214-216]. In food formulations, the PL fraction of the egg yolk participates in the stabilization of the system through its emulsifying properties. The TAG fraction is integrated in the dispersed oil phase forming lipid droplets.

Besides their interest in structuring formulated food at a colloidal scale, lipid structures of the egg and egg products can develop specific nutritional interest with respect to two main applications. One is related to the significant dietary supply in omega-3 long chain FA located on PL (in particular on PE) they can represent. The other one, is the ability of egg yolk lipoproteins to improve the bioavailability of some lipophilic micro-constituents as compared to other delivery systems. For instance, after 9 days of testing, for similar amounts ingested, the amount of lutein in the serum of adults was higher after egg consumption than after lutein supplements or spinach consumption [217]. Moreover, egg yolk and its constituents (phospholipids and endogenous antioxidants, such as the endogeneous phosphorylated protein, phosvitin) can protect formulated food against oxidation [218].

4.1.4. Organization of lipids in oilseeds

In oilseeds, lipids are stored in organites called oleosomes [219]. Oleosomes are constituted by a hydrophobic core rich in TAG surrounded by a monolayer of PL and proteins (mainly oleosins and caleosines) [220]. The oleosins have strong steric hindrance. This organization ensures the oleosomes very high stability against thermal or detergents injuries [221]. The size of oleosomes

varies with the species: rapeseed (0.65 µm), linseed (1.34 µm), peanut (1.95 µm). The neutral lipids, mainly TAG, account for more than 94% while phospholipids and proteins vary from 0.4 to 2% and from 0.5 to 4%, respectively [222]. The phospholipid composition of oleosome varies according to species though PC is the major form. For example, PC content (expressed as wt% of total phospholipid) is 60% in rapeseed [222] and 80% in sunflower [223]. In rapeseed and linseed [222], the high proportion of PS, 20% and 33% of total phospholipid respectively, is an interesting factor because it is a major phospholipid of brain and nerve structures. Various studies have highlighted the positive effect of PS supplementation to limit memory loss associated with aging, enhance cognitive performance and improve the behavior of people with Alzheimer's disease [224-228].

The structure of the oleosomes completely disappears during the industrial processes of oil extraction and oilseed lipids are mainly consumed in the form of bulk oils or present as an ingredient in various formulations where they are emulsified. Refined oils only contain the oilseed TAG. It is however possible to produce oils containing phospholipids by using a partial refining that avoids the steps of degumming. These phospholipid-containing oils exhibit emulsifying properties. Studies are in progress to develop new techniques of extraction preserving the native structure of the oleosomes to be used as functional ingredients [229].

4.2 Impact of emulsified structures on digestion, absorption and metabolism of FA

The dispersion of lipids in the form of droplets, the size of the lipid droplets and the composition of their interface may affect the kinetics of lipid digestion and absorption as previously reviewed [123, 230, 231].

4.2.1. Emulsified vs non-emulsified lipids

In rats the absorption of sunflower oil was enhanced by emulsification, the droplets being stabilized with lecithin [232]. In humans, the levels of plasma TAG (postprandial area under the curve during 9 h) and that of PUFA in plasma lipids, mainly EPA and DHA, were higher after ingestion of an emulsified oil compared to the same oil ingested in the non-emulsified state while the effect on plasma TAG was not observed on the saturated or short chain FA [233]. One must note that the lysophospholipids, provided by the soya lecithin used to stabilise the emulsions improved the velocity and amounts of the FA released in rat lymph by modifying the absorption and/or secretion process at the enterocyte level [234-236].

In humans the absorption of *n*-3 FA, evaluated from the FA composition of plasma PL for 48 h after ingestion, was enhanced after the ingestion of a single dose of fish oil given emulsified, as compared with non-emulsified (capsule) [237]. The authors hypothesis that emulsification favoured the action of digestive lipases by simplifying the emulsification that occurs in the stomach, as previously stated [238]. Most recently, the enhancement of FA absorption by emulsification also resulted in enhanced beta-oxidation of exogenous FA in lean and obese humans [239].

Emulsions are also widely used as carriers for lipophilic micronutrients or bioactive molecules [240, 241]. This topic has recently been reviewed in detail [242, 243]. Regular oil-in-water emulsions are the most commonly used to encapsulate lipophilic molecules such as *n*-3 PUFA, carotenoids and phytosterols, but more complex emulsions such as multiple emulsions or multi-layered emulsion droplets have been also proposed [240, 244].

4.2.2. Size of emulsion droplets

In vitro studies revealed that the level of TAG hydrolysis by gastric and pancreatic lipases is higher for small droplets compared to large droplets (0.5 *vs* 3 µm), as a result of a higher interfacial area accessible to enzymes [245, 246]. A recent study performed with native milk fat

globules of various sizes (1.6 *vs* 4 *vs* 6.7 µm) showed that the hydrolytic efficiency of the human pancreatic lipase *in vitro* is higher on small *versus* large native milk fat globules [247]. The catalytic efficiency of the human pancreatic lipase is also higher on homogenized milk fat globules (0.14 to 1.4 µm) than on native milk fat globules [247]. *In vivo* in the rat, the level of lipid hydrolysis was higher for small droplets compared to larger ones (0.8 *vs* 22 µm) [238]. However, the absorption of vitamins A and E did not depend on the size of emulsified lipid droplets [248]. In humans, the hydrolysis of TAG by gastric and pancreatic lipases was more efficient with droplets of small size (0.7 *vs* 10 µm) containing, among others, fish oil, olive oil and soya lecithin [249]. The time required for gastric emptying was longer for the emulsions containing the smallest droplets. During the kinetics of postprandial lipemia, the peak of plasma TAG and their clearance to tissues were delayed [238, 249]; the metabolic impact remains nevertheless to be studied.

4.2.3. Composition of the interface

The composition of the TAG/water interface is an important parameter controlling the efficiency of TAG hydrolysis. Recently, *in vitro* studies revealed that the activity of the human gastric lipase is higher when the lipid droplets are covered by PC, PI or PS compared to PE and SM [250]. Moreover, the presence of whey proteins or caseins at the surface of the oil droplets enhanced the action of the lipases [17]. However, the presence of these milk proteins at the milk TAG/water interface was less favourable to hydrolysis than the native biological MFGM [247]. Still *in vitro*, the lipolysis by pancreatic lipases of soya oil droplets was enhanced when the droplets were stabilised by proteins (whey proteins and sodium caseinate) instead of lecithin (unspecified PL composition) [251]. Other data underlined that the nature of the emulsifier adsorbed at the surface of emulsion droplets affects the structural changes of the emulsions along the digestive tract [252]. Using another *in vitro* digestion model including both gastric and pancreatic lipases, emulsions formulated with soybean lecithin (13% PC, 30% PE, 25% PI, 23% Lyso-PL) as

emulsifier had enhanced lipolysis compared emulsions stabilised with sodium caseinate [253]. This is consistent with a recent human study showing that emulsion formulated with sodium caseinate + MAG resulted in a lower postprandial triglyceridemia than emulsion formulated with polyoxyethylene sorbitan monooleate (Tween-80) [254]. Of note, different dairy proteins (e.g. native casein micelles *vs* sodium caseinate *vs* whey proteins) present various structures and adsorption profiles at lipid/water interfaces, the consequences of which on gastrointestinal lipolysis should be further investigated *in vivo*.

4.2.4 Milk fat globules as natural emulsion droplets

The processes applied to transform milk in dairy products may have consequences on the digestion of milk fat by modifying its emulsified organisation and the composition of the TAG/water interface [186]. This could explain why in premature infants, during the gastric phase, the lipolysis of native human milk fat globules is greater than homogenised milk fat globules, despite the smaller size of the fat globules [255]. *In vitro* studies reported that both the size of milk fat globules and the composition of the milk TAG/water interface (native biological membrane *vs* milk proteins) affect the catalytic efficiency of the human pancreatic lipase [247, 256]. These studies highlight the crucial role of the native MFGM in the efficiency of the digestion of milk fat globules.

In the rat, the supramolecular organization of milk fat was reported to affect the digestion and post-absorptive beta-oxidation process of FA [257, 258]. Non-emulsified milk fat and milk fat emulsified in the form of large droplets mainly covered by PL (10 µm), both labelled with ^{13}C-TAG tracer, lead to the formation of a sharp $^{13}CO_2$ secretion peak after 1 hour and to its rapid decrease. Conversely, an emulsion composed of small droplets (1 µm) mainly covered by caseins led to a more progressive $^{13}CO_2$ secretion up to 6 hours after fat ingestion [257]. It was hypothesized that the time for gastric emptying could be longer for the emulsion containing the small droplets covered by caseins due to clotting in the stomach. These authors also compared

milk fat ingested as different suprastructures and measured the postprandial kinetics of plasma TAG [258]. The appearance of plasma TAG was delayed for native milk fat globules (4 µm) covered with their biological membrane compared to non-emulsified milk fat. After 180 minutes (corresponding to the plasma TAG peak), plasma TAG (i) decreased logarithmically when the surface of fat globules increased and (ii) were lower for the homogenised fat globules (1 µm) covered by caseins compared to the native fat globules and the unemulsified milk fat.

5. Supramolecular level: the food matrix modulates fatty acid metabolism

5.1 Lipid accessibility in food matrixes

Dietary lipids need to be accessible to digestive enzymes so that their digestion and absorption can occur. The accessibility of TAG to lipases can be hindered by the characteristics of the food matrix, including their composition, supramolecular structure and mechanical behaviour. The food matrix, which can be composed of proteins, sugars, starch and fibres, is destroyed during mastication, diluted and dissolved by saliva and gastric juice and hydrolysed by the digestive enzymes, which allows the release of the embedded lipids and/or the access of the lipases to their substrates. This is why both the composition and the structure of food matrix may affect the biodisponibility of dietary lipids.

Authors reported that the strong resistance of almond cell walls limits the release of lipids and that their level of absorption increases with a higher degree of mastication [259-261].

The viscosity of food products can also affect the digestibility of lipids [262]. Higher viscosity increases the time for gastric emptying and delays the peak of plasmatic TAG during the postprandial period, e.g. for cream cheese with high viscosity *vs* liquid cream [263] and for milk *vs* fermented milk that is more viscous [264].

Food matrixes can thus be designed to control the release and the bioavailability of lipids [265]. For instance, edible films composed of soya proteins to regulate the release of hydrophobic molecules during digestion [266]. The encapsulation of droplets of micronic size composed of vegetable oil in a starchy matrix has also been described [267, 268].

5.2 The interactions of the non-lipid components of the matrix with fatty acid metabolism

5.2.1 Interactions with carbohydrates

Dietary carbohydrates can be divided in two categories: (i) digestible carbohydrates (sugars, starch) and (ii) non-digestible carbohydrates (mainly fibres). They play an important role in digestion and absorption of lipids, the mechanisms of which have been reviewed [269]. Clinical studies show that the presence of sucrose [270] and fructose [271] increased the level of plasmatic TAG after a diet rich in dietary lipids. The presence of glucose delayed the secretion of chylomicrons and decreased the level of TAG associated to VLDL [272, 273]. In contrast, the presence of starch in the diet did not affect the postprandial lipaemia [274] whereas the addition of dietary fibres decreased the postprandial lipaemia [275]. Several mechanisms have been proposed to explain the impact of carbohydrates on the digestion, absorption and metabolism of dietary lipids. Glucose, oligosaccharides and some fibres affect the time for gastric emptying [269]. The fibres, by increasing the viscosity of the bolus, would limit the extent of lipid emulsification in the stomach and thus slow down lipolysis [276, 277]. It has been also proposed that some dietary fibres could have an inhibitory effect on pancreatic lipases [278, 279]. The reader will find detailed information on this topic in specific reviews [269, 280].

5.2.2 Interactions with proteins

The interactions of dietary proteins with regulatory functions of the gastrointestinal tract have profound effects on physiologic and metabolic responses, e.g. through their satieting effect. Most of the studies about lipid metabolism concerned concentrations of plasma cholesterol depending on the protein type (whey proteins, caseins, egg white, soy protein, beef and fish proteins but also protein hydrolysates), as reviewed [281]. Some studies reported indications in relation to plasma TAG concentration. Lower cholesterol content in HDL and lower plasma TAG were found in rats after 22 days of a diet containing fish protein compared to casein diet [282]. Lower plasma cholesterol and TAG were found in rats receiving cholesterol-enriched diets containing both caseins and soya proteins (15% and 5% respectively) instead of caseins alone (19.7%) [283]. The decrease in plasma cholesterol has been explained by the hydrophobicity and bile acid binding capacity of the proteins [284] or the amino acid profile regarding the presence of cystein [285]. However, in rats receiving diets rich in saturated fat and containing either total milk protein, rapeseed proteins or total milk protein + cystein + argine, the increase in plasma TAG during postprandial period was similar for the three diets [286]. The absence of impact of the cystein content of dairy proteins on plasma TAG was confirmed in humans [287]. These authors found a lower increase in plasma TAG for casein diet compared to whey proteins diet and whey proteins supplemented with α-lactalbumin. Cystein (but also arginine) content would rather modify vascular and oxidative effects. A lower postprandial lipaemia was also reported with the presence of caseins in a diet rich in lipids for healthy subjects [288]. Moreover, the consumption of a diet rich in proteins decreased the amount of TAG associated to the chylomicrons during the postprandial period [289]. In patients with a type-2 diabetes, whey proteins led to a lower increase of the postprandial lipaemia compared to casein, gluten and cod proteins [290].

5.2.3 Interactions with minerals

Minerals present in the matrix can also impact on lipid digestion and metabolism. Long-chain saturated FA released during the hydrolysis of TAG are able to form, with the dietary divalent cations (mainly calcium but also magnesium), unsoluble soaps that are excreted in the faeces [291]. An increase in the dietary calcium decreased accordingly the absorption and increased the excretion of lipids in the faeces, in the rat and in humans [292-296]. The high amount of calcium in dairy products limits the intestinal absorption of saturated FA in humans [292, 297]: increasing calcium intake of about 1500 mg/j through low-fat dairy products results in an average increase of 5 g lipids excreted in stools. Calcium and more specifically dairy calcium have been shown to produce decreases in body weight and body fat in several observational [298, 299] and intervention studies [300-303], but not in all studies [304-307]. Therefore, long-term studies are required to establish the contribution of dairy calcium to energy balance and potentially to weight loss. Probably due, at least in part, to the increased faecal excretion of saturated fatty acids, dairy calcium may also affect lipid profile [294, 308]. We must remember that the effect of calcium on the lowering of FA absorption greatly depends on the structure of TAG because only the FA hydrolysed in the *sn*-1 and *sn*-3 positions are able to form soaps in the intestine and be excreted in the faeces [53, 309]. The many other factors that can affect soap formation during digestion, e.g., gastric pH, phosphate presence and structure, duodenal interaction between SFA and calcium, proteins etc have recently been reviewed [308].

5.3 Present knowledge on the impact of food matrix gained from dairy and fish products

In the rat, kinetic profiles of postprandial FA lymphatic absorption depended on dairy products (butter, mixed butter, cream, sour cream, cream cheese) characterised by a similar FA

composition but different viscosities, structure of fat and protein amounts [263]. The cumulated absorption was lower with butter compared to cream and cream cheese. In patients with type 2 diabetes, the cumulated amounts of postprandial plasma TAG after 6 hours were similar after consumption of butter, mozzarella and milk (30 g of fat), but butter delayed the peak [310]. The rate of gastric emptying did not seem to be involved in this delay, but rather the viscosity and the dispersion state of lipids (native milk fat globules in milk, aggregated milk fat globules dispersed in a protein matrix for mozzarella, free fat for butter). In healthy humans, the consumption of 40 g of lipids (butter) led to a lower level of plasma TAG during the 7 hours of the postprandial period compared to olive oil and sunflower oil emulsified in a sausage [311]. However, the TAG peaks were observed at similar times. The authors primarily underlined the different FA compositions, but the emulsification state of TAG and the solid state of butter *vs* liquid oil are other parameters that could partially explain the results. In a crossed randomized study, healthy subjects consumed for 3 weeks well-controlled diets with 20% of the energy provided by milk fat in the form of milk, butter or hard-type cheese [312]. A digestion test performed the 4^{th} day of each period did not reveal any difference in the amount and composition in FA of the chylomicrons during the 8 hours of the postprandial period. As many components (PL, minerals, proteins…) of the diets could have affected the postprandial lipemia, the results cannot be attributed to only the suprastructure of the lipids.

Altogether, the impact of the structure of dairy product on lipemia and health remains controversial and presently published results deserve further research in this field [16, 239, 313].

Regarding fish products, numerous clinical and epidemiological studies have shown that the consumption of fat-rich fish or capsules of fish oil rich in *n*-3 has a protective effect against the cardiovascular diseases. However, the doses provided with the dietary complements are generally much higher than those brought by the diet [314], although a low intake of fat-rich fish is sufficient to observe beneficial cardiovascular effects [315, 316]. In human, *n*-3 PUFA (EPA and DHA) consumed in salmon were better absorbed and incorporated in plasma lipids than similar

amounts in the form of capsules of ethyl esters [317]. Interestingly, the nature of the molecules was also different between both groups: TAG and some PL *vs* ethyl esters. Also, *n*-3 FA were better incorporated in plasma lipids when consumed from salmon *vs* cod liver oil, even if the latter provides a daily intake of EPA + DHA 3-fold higher compared to salmon [318]. Similar effects were observed on plasma lipids and lipoproteins after the consumption of fish or fish oil by hyperlipidemic subjects [319]. It has been suggested that the better absorption of *n*-3 FA results from the dispersed state of TAG in fish [318]. However, we cannot rule out a possible effect on the entire structure of this food matrix. In a recent review, the differences between the regular consumption of fish and the consumption of dietary complements as sources of *n*-3 FA were discussed [320]. These authors highlighted the potential role of other components of fish, of their possible contamination and of the possible impact of cooking on the lipid composition of fish.

Information on the effect of food matrix on lipid metabolism in other types of food products is scarce. Many natural food products present complex structures of lipids and other nutrients whose specific effects should be compared with those of formulated foods or dietary supplements.

5.4 New insight: possible consequences of oral fat perception from different food products on lipid absorption

We must point out recent advances in the link between oral fat perception in foods on a sensory standpoint and digestive signals that might alter lipid postprandial digestive response. In the mouth, lipase activity is much too low to be significant for digestion *stricto sensu*. However, recent studies reveal its importance in the orosensory detection of fat through the generation of low amounts of FFA [321-323]. In rodents, the presence of the lipid sensor CD36 in taste bud cells was revealed; it is involved in oral perception of free FA and enhances the release of digestive secretions [324]. GPR120 has then been pointed out as being another receptor involved in long-chain FA sensing [325]. As recently reviewed, the pharmacological inhibition of lipolysis

in rodents blunts these phenomena, which shows the link between FA release by lipase in the mouth and further FA detection by dedicated receptors [326]. Most importantly, CD36 gene is also specifically expressed in taste bud cells in humans [327]. A role of CD36 in fat gustatory perception in humans was evidenced, supporting an involvement of lingual lipase throught the generation of FA stimulus [322]. These data can contribute to explain the findings that in humans, (i) hypersensitivity to lipids in the mouth was associated with lower fat intake, lower energy consumption and lower BMI [328] and (ii) saliva characteristics such as lipolysis, lipocalin and flow are correlated with fat-liking or perception [323].

Importantly, such oral fat detection of lipids can impact on their postprandial process in the gut and their absorption. As studied [329-332] and reviewed [333], digestive secretion, lipid intestinal absorption, enterocyte storage and mobilization are affected by oral stimulation induced by the fat amount of food products. Oral perception of a high-fat stimulus enhanced (i) the secretion of the intra-enterocyte TAG pool from the previous meal and (ii) postprandial lipemia compared with a low-fat stimulus [329, 332]. As detailed above, the structure of the lipids in the food matrix can modify digestive lipolysis by mechanisms involving lipase access and activity at the lipid interface. Lipid and food matrix structure may also modify the release of FFA in the mouth through oral lipolysis. We thus raise the question of how such lipid and food structures can affect lipid sensor-mediated oral fat detection and subsequent signal transmission regarding digestive secretions and processing.

6. Conclusion

This review highlights the possible impacts on FA intestinal absorption and post-absorptive metabolism of the lipid structures, evaluated at scales ranging from the molecular to the supramolecular ones, including their interactions with the food matrix. These possible nutritional

impacts could be now kept in mind in the development of new food formulations with enhanced taste and texture. It remains that the metabolic data obtained in humans are, to date, limited. To improve the level of proof and demonstrate the effects in humans, clinical trials including dietary interventions should now be conducted. These trials will highlight and allow to quantify the potential benefits of the native or recomposed lipid structures. This will allow designing new food formulations with optimized metabolic fate of lipids regarding FA bioavailability and their handling by tissues. Multidisciplinar collaborative projects including specialists of food processing and food science, biochemists, physico-chemists, nutritionists and clinical scientists should now address these challenging issues.

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Figure caption

Figure 1. Summary of the various molecular & supramolecular structures of lipids in food products. Adapted from [334, 335].

Figure 2. Importance of supramolecular and triacylglycerol structures on digestion and postprandial lipemia. Highly schematized; adapted from [16, 334, 336].

Figure 3. Thermal behavior of different fats and oils: (A) examples of melting profiles of milk fat and palm oil highlighting their different melting temperature (C. Lopez, personal communication). (B) correlation between the solid fat content (SFC) of fat at 5°C and major triacylglycerol species (PSO: 16:0/18:0/18:1, regardless of regiodistribution of these fatty acids; OOO: 18:1/18:1/18:1, triolein) in different products from 2 origins: pork (lard *vs* rillettes) and duck (fat extracted from foie gras *vs* rillettes); adapted from [337].

Table 1. Positional distribution of fatty acids (mol%) in TAG of common fats and oils.

Adapted from original data [38, 338] and previous reviews [16, 334, 339, 340].

		FA regiodistribution on TAG*								
Fats & oils (Main TAG species)	*sn*-position on TAG	Butyric acid (4:0) and caproic acid (6:0)	Caprylic acid (8:0)	Capric acid (10:0)	Lauric acid (12:0)	Palmitic acid (16:0)	Stearic acid (18:0)	Oleic acid (18:1 *n*-9)	Linoleic acid (18:2 *n*-6)	α-linolenic acid (18:3 *n*-3)
Cocoa butter (POS, SOS, POP)	*sn-1*				-	47	48	11	10	ns
	sn-2				-	3	2	81	90	ns
	sn-3				-	51	50	8	Traces	ns
Palm oil (POP, POO, POL)	*sn-1*					41	27	25	30	ns
	sn-2				17	9	Traces	62	60	ns
	sn-3					50	73	13	10	ns
Peanut oil (OOL, POL, OLL)	*sn-1*				-	52	50	34	28	ns
	sn-2				-	7	Traces	34	57	ns
	sn-3				-	41	50	33	15	ns
Milk fat (OPBu, PPBu,PMyBu)	*sn-1*					44,5	56	59		
	sn-2		43.5	51.5	60	43	16	0	35	44
	sn-3	>93	52.5			12.5	28	41		
Lard (SPO, OPL, OPO)	*sn-1*				ns	23	54	43	35	ns
	sn-2				ns	61	8	13	26	ns
	sn-3				ns	16	38	44	39	ns
Beef tallow (POO, POP, PSO)	*sn-1*				ns	51	34	20	29	ns
	sn-2				ns	21	18	42	36	ns
	sn-3				ns	28	48	38	36	ns

* % of FA on each sn-position = mol of FA on the specified sn-position per 100 mol of this FA in all TAG.
Void cells: complement to 100 for the FA considered (e.g. in palm oil, 83% of total 12:0 is located on external *sn*-2,3 positions).
ns : distribution not specified (minor FA in the total FA composition).
- : FA not detected in this oil or fat.
Bu: butyric acid, L: linoleic acid, My: myristic acid, O: oleic acid; P: palmitic acid, S: stearic acid

Table 2. Fatty acid compositions and melting points of various dietary oils and fats [341].

Fatty acids	% FA								
	Milk fat	Lard	Copra oil	Palm oil	Sunflower oil	Rapeseed oil	Olive oil	Soybean oil	Peanut oil
4:0	3-4								
6:0	2-3		<1						
8:0	1-2		6-10						
10:0	2-4		5-10						
12:0	3-4		39-54	<0.2					
14:0	9-12	1.3-1.8	15-23	1-2			<0.1	<0.2	
14:1 (n-5)	1-2	<1							
15:0	1-2	0.1-0.2							
16:0	23-32	23-26	6-11	43-46	5-7	4.5	8-21	8-13	8-13
16:1 (n-7)	2-3	1.4-3.7	<2	<0.3	<0.4	0.6	<4	<0.2	<0.3
18:0	10-12	12.8-18.0	1-4	4-6	4-6	1.5	1-6	2-5	1-4
18:1 (n-9)	29	39-45	4-11	37-41	15-25	60.5	53-80	17-26	35-66
18:2(n-6)	2-3	8.5-12.0	1-2	9-12	62-70	21.5	3-24	50-62	14-41
18:3(n-3)	<1	0.5-1.5	<0.1	<0.4	<0.2	10.3	<2	4-10	<0.3
20:0	<0.2	0.0-0.3	<0.2	<0.4	<1		<0.5	<1.2	1-2
20:1		0.5-1.3	<0.2		<0.5	0.9	<0.4	<0.4	1-2
22:0					<1		<0.9	<0.5	2-5
22:1						0.2			
Melting Point (°C)	35 to 40	32 to 38	23 to 26	27 to 45	-17	-10 to 2	-6	-16 to -10	3