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The Complex and Important Cellular and Metabolic Functions of Saturated Fatty Acids

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Abstract This review summarizes recent findings on the metabolism and biological functions of saturated fatty acids (SFA). Some of these findings show that SFA may have important and specific roles in the cells. Elucidated biochemical mechanisms like protein acylation (N-myristoylation, S-palmitoylation) and regulation of gene transcription are presented. In terms of physiology, SFA are involved for instance in lipogenesis, fat deposition, polyunsaturated fatty acids bioavailability and apoptosis. The variety of their functions demonstrates that SFA should no longer be considered as a single group.

Keywords Dietary saturated fatty acids · Myristic acid · Metabolism · N-myristoylation

Abbreviations

FA	Fatty acids
NMT	Myristoyl–CoA: protein N-myristoyltransferase
PL	Phospholipids
PUFA	Polyunsaturated fatty acids
SCD	Stearoyl–CoA desaturase
SFA	Saturated fatty acids
TAG	Triglycerides

Introduction

Observational studies have shown that high intake of saturated fatty acids (SFA) is positively associated with increased levels of blood cholesterol and high coronary heart disease mortality rates [1, 2]. However, more recent studies have shown inverse association [3, 4], and the meta-analysis by Siri-Tarino et al. [5] reopened the debate when writing that "there is no significant evidence for concluding that dietary saturated fat is associated with an increased risk of CHD or CVD". Without entering this interesting epidemiological debate on the deleterious effects of some of saturated fatty acids, it seems that they can be no longer considered as a single group in terms of structure, metabolism [6, 7] and cellular function. In this context, this review will focus only on recent findings suggesting that individual SFA possess specific properties associated with important biological functions.

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New Aspects on the Metabolism of Saturated Fatty Acids

Cellular Origin of Saturated Fatty Acids

SFA usually account for 30–40% of total FA in animal tissues, distributed in palmitic acid (15–25%), stearic acid (10–20%), myristic acid (0.5–1%) and lauric acid (less than 0.5%). Palmitic and stearic acids are universally found in natural fats. Lauric acid is specifically abundant in copra (39–54%) and palmist oils (44–51%). Myristic acid and short-chain fatty acids (including butyric acid) represent each about 10% of FA in milk fat. Apart from the dietary sources, it is well known that the body is capable of synthesizing SFA. Because of their multiple potential origins, it has been difficult to quantify the real importance of dietary SFA when compared with endogenous SFA, especially for palmitic acid. Adipose tissue concentrations of C15:0, C17:0 but also C14:0 have been used as quantitative

markers of dairy consumption [8]. With regard to myristic acid, the amount of its endogenous biosynthesis [9] is indeed far smaller than the amounts consumed from dietary sources (4 g/day in a Swedish population) [10].

Desaturation of Saturated Fatty Acids

Recent findings on SFA concern their respective capacities to be desaturated. Every SFA from C12:0 to C18:0 is converted to its respective monounsaturated product through the action of Δ9-desaturase (Stearoyl–CoA desaturase, SCD) but with varying efficiency. In the rat [11], a clear increase in hepatic Δ9-desaturase activity is related to the carbon chain length, from C12:0 to C18:0. Evidence was also recently presented that palmitic acid, already known as a substrate of Δ9-desaturase, can also be desaturated by the mammalian Δ6-desaturase (Fatty acid desaturase 2: FADS2) [12]. Palmitic acid Δ6-desaturation produces sapienic acid (C16:1n-10) in the preputial gland of SCD1−/− mice [13] and in human sebaceous glands in which the expression of SCD is low [14]. The importance of this human physiological specificity remains to be determined.

Specific Biochemical Functions of Individual SFA

Regulation of Protein Activation by N-terminal Myristoylation

Myristic and palmitic acids are directly involved in the two classes of protein fatty acid acylation, N-terminal myristoylation and side-chain palmitoylation [15]. Protein N-myristoylation (Fig. 1) refers to the highly specific covalent attachment of myristic acid, by an amide linkage, to the NH_2-terminal glycine residue of increasing number of eukaryotic and viral proteins [16]. Myristoyl–CoA: protein N-myristoyltransferase (NMT, EC 2.3.1.97), the enzyme catalyzing this stable acylation, has been identified in many organisms. Genetic advances have revealed that mammals possess two distinct NMT genes, named type 1 and 2 [17–19]. The contribution of each gene transcript to NMT expression and activity in vivo, and the specific role of each NMT isoform in cellular replication, proliferation, and other cellular processes, is still under investigation [20–22]. They both seem to have a similar high substrate selectivity for myristic acid [17, 19]. The myristoyl moiety has been shown to mediate protein subcellular localization, protein–protein interaction or protein–membrane interactions (Fig. 1) required for the biological activities of the myristoylated proteins [16]. In the myristoylation pathway, myristic acid therefore exhibits a specific and important role for protein activation.

The proteins that are substrates of NMT include key components in intracellular signaling pathways, oncogenes, structural viral proteins, and common constitutive eukaryotic proteins. Computational prediction recently suggested that about 0.5% of all proteins in the human genome could be myristoylated [23]. New protein substrates identified recently in mammals are the tumor suppressor Fus1 [24], TRIF [25], the sphingolipid Δ4-desaturases type 1 and 2 [26], and truncated protein forms that become substrates after post-translational cleavage by caspases that reveals an internal myristoylation motif: BID [27], actin [28], gelsolin [29], and p21-activated protein kinase 2 [30].

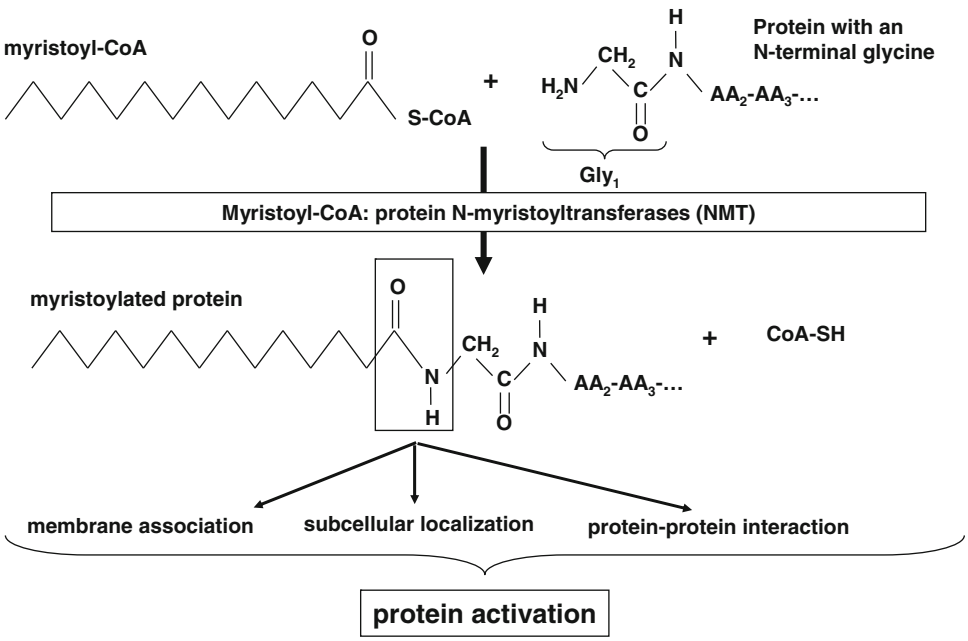

Fig. 1 N-terminal myristoylation of proteins with myristic acid by myristoyl–CoA: protein N-myristoyltransferases (*NMT*) and biological consequences for the myristoylated proteins

Can Myristic Acid be the Rate-Limiting Molecule in the Myristoylation Pathway?

Since endogenous biosynthesis of C14:0 [9] is very low as compared with dietary sources [10], one can ask if the amount of free myristic acid could be insufficient to provide myristoyl–CoA: protein N-NMT with enough co-substrate. In yeast, studies analyzing the activity of NMT have suggested that the enzyme was able to use both exogenous and endogenous myristic acid as the substrate [31–33]. During the process of the maturation of one protein, the pool of endogenous free myristoyl–CoA would probably be sufficient [34]. However, when considering the pool of myristoylable proteins or the specific process for the maturation of viral proteins like Gag or Nef during the course of a viral, retroviral or lentiviral infection, the amount of myristoyl–CoA co-substrate needed is considerable [35]. The requirement for myristic acid suggests that in certain cases, it could be the rate-limiting molecule in this mechanism or that competition could occur. In addition, the mechanism by which myristic acid initially esterified in the TAG or PL is used for myristoylation is unknown, too. The available evidence indicates that the intracellular concentration of free myristic acid in endothelial cells is crucial for the activation of thrombospondin-1 and could be modulated by its uptake from the medium through CD36 [36].

Regulation of Protein–Membrane Interactions by Palmitoylation

Protein palmitoylation refers to the post-translational formation of a thioester linkage between the side-chain of cysteine and palmitic acid, mainly [37], or other saturated fatty acids, like myristic and lauric acids [38]. A long time ago, the ester linkage between saturated fatty acids and serine or threonine residues was also reported [39], but since then, this type of linkage has not been described again.

Palmitoylation is involved in regulatory mechanisms because the association of the protein with the palmitoyl moiety is reversible and facilitates protein–membrane interactions and subcellular trafficking of proteins. Several signal transductions depend therefore on palmitic acid, including proteins that have been shown to undergo successive myristoylation and palmitoylation, like the α subunit of many heterotrimeric G proteins [40]. Mammalian protein palmitoyltransferases (also named Protein S-AcylTransferases PAT) are still under investigation [37]. The recent biochemical evidence of the PAT activity of a family of proteins that share a DHHC motif in yeast [41–43] has opened a new field of investigation.

Regulation of Gene Transcription by Saturated Fatty Acids

While dietary PUFA are known to regulate gene expression through their influence on transcription factors (PPAR, SREBP), the effect of SFA on gene transcription has been less explored. Lin et al. [44] have shown that SFA (C10:0–C18:0) strongly elevate the PGC-1β mRNA level, that co-activates the action of SREBP family of transcription factors, and consequently increase the transcription of lipogenic target genes (*FAS*, *SCD-1*). Co-activation of the nuclear receptor LXR/RXR also promotes VLDL secretion. SFA (but also monounsaturated FA) are known to bind hepatocyte nuclear factor 4 (HNF4). In liver cells, palmitate and oleate both enhanced the transcription of glucose-6-phosphatase gene. Palmitate also induced the recruitment of several transcription factors like NF-κB, HNF4, CEBPα, and PPARα [45]. SFA, when linked to the lipid A moiety of lipopolysaccharides, or free, also indirectly induce NF-κB nuclear translocation, activation and expression of COX-2, and other pro-inflammatory cytokines, through the recently described toll-like receptor 4-derived signaling pathways [46, 47]. Finally, because it is an inhibitor of the histone deacetylase activity, butyric acid regulates the expression of several genes, like *IL5*, by altering the histone acetylating status of their promoter regions, with consequences for the structure of chromatin [48, 49].

New Demonstrated or Putative Physiological Roles of SFA

Stearic Acid is Neutral for Cholesterol but Could be Pro-Lipogenic

As for the other long-chain saturated fatty acids, the health impact of stearic acid has been studied, showing no deleterious effect on cardiovascular disease risk [50, 51]. The high rate of C18:0 conversion to C18:1n-9 by Δ9-desaturation was suggested to explain this neutral effect on cholesterol metabolism, compared to the other SFA [52]. On the other hand, the desaturation of dietary stearate to endogenous oleate has been described as a stimulating factor for VLDL–TAG secretion in hepatocytes [53], and an essential step mediating the induction of lipogenesis [54] and the promotion of obesity [55], showing the very important role of SCD. The evidence concerning the putative effect of stearic acid on thrombotic tendency appears inconsistent [56, 57].

Myristic Acid Could Regulate PUFA Bioavailability

It has recently been suggested that myristic acid may be an activator of the conversion of α-linolenic acid to

docosahexaenoic acid (DHA). In cultured rat hepatocytes, myristic acid had a specific and dose-dependent effect on Δ6-desaturase activity [58]. In vivo, when myristic acid was supplied for 2 months in the diet of rats (from 0.2 to 1.2% of dietary energy), with similar level of dietary α-linolenic acid (1.6% of FA, 0.3% of energy), a dose–response accumulation of eicosapentaenoic acid (EPA) was shown in the liver and plasma [59].

In addition, in humans, compared with a diet containing 0.6% of myristic acid mainly in the *sn*-2 position in the TAG, a diet containing 1.2% of myristic acid during a 5-week consumption period significantly enhanced EPA and DHA levels in the plasma PL and DHA level in the plasma cholesteryl esters [60]. When the intake of myristic acid increased from 1.2 to 1.8% energy in the same population, EPA, DPA and DHA decreased significantly in plasma PL and EPA also decreased in cholesteryl esters [61]. This result suggest that, in humans, the effect of myristic acid on circulating (n-3) PUFA follows a U-shaped curve with a favorable turning point at around 1.2% of total daily energy.

So far as potential mechanism(s) of action are concerned, the increase in the activity of Δ6-desaturase by myristic acid was first postulated to be mediated by N-myristoylation (see below) because this enzyme exhibits an N-terminal glycine residue. However, we recently demonstrated that Δ6-desaturase is not myristoylated in vivo [26]. The hypothesis has been proposed that myristoylation of another protein of the whole complex of Δ6-desaturation, NADH cytochrome *b*5 reductase [62], could account for this increased activity.

Lauric Acid Could be a Precursor for ω3 Fatty Acid Biosynthesis

The low level of C12:0 conversion to C12:1n-3 in the liver of rats has led to the hypothesis that this monounsaturated fatty acid of the (n-3) series might be, under extreme physiological circumstances [for example animals deprived of (n-3) PUFA in the diet during a long period], an unusual precursor for the biosynthesis of α-linolenic acid, by successive Δ6-desaturation, elongation, Δ5-desaturation and two final elongations [11].

SFA May Play Multiple Roles in Early Events of Apoptosis

Specific histone deacetylase inhibitors, like butyric acid, selectively induce cellular differentiation, growth arrest and apoptosis in a variety of cancer cells [63]. Although contradictory effects have been reported [64], it seems that delivery of an adequate amount of butyrate to the appropriate site could protect against early tumorigenic events [65].

Several SFA may induce apoptosis via different ways. First, as already suggested above, butyrate and short-chain SFA may also have an effect on apoptosis [66]. Second, the pro-apoptotic effect of non-esterified palmitate and stearate was shown to require acyl–CoA formation and NF-κB activation [67]. Third, SFA may also influence apoptosis via the ceramide pathway by inducing ceramide de novo synthesis at several steps [68–70]. The first step catalyzed by the serine palmitoyltransferase involves serine condensation with palmitoyl–CoA [71]. The last step is catalyzed by dihydroceramide Δ4-desaturase (DES). We recently showed that both DES1 and DES2 isoforms are myristoylated and that this N-terminal modification significantly increased the activity of recombinant DES1 in COS-7 cells [26]. Compared with a recombinant unmyristoylable mutant form of DES1 (N-terminal glycine replaced by an alanine), the desaturase activity of the myristoylable wild-type DES1 was two times higher, in the presence of myristic acid incubated with the cells [26]. The description of this regulatory mechanism highlighted a new potential relationship between myristic acid, the saturated fatty acid capable of binding and activating the enzyme involved in the final de novo ceramide biosynthesis step, and lipoapoptosis induced through the ceramide pathway. Therefore, we subsequently hypothesized and showed that the myristoylation of recombinant DES 1 can target part of the enzyme to the mitochondria, leading to an increase in ceramide levels (specifically in the mitochondria) which in turn leads to apoptosis in the COS-7 cell model [72].

Medium-Chain Fatty Acids and Fat Deposition

A point of interest is the specific role played by medium-chain SFA. It has been reported that overfeeding with a medium-chain TAG diet in rats results in a diminished deposition of fat, when compared with rats overfed with isocaloric long-chain TAG [73]. This suggests an obligatory oxidation of medium-chain SFA in the liver, after transport via the portal vein, leaving no medium-chain TAG for accumulation in adipose tissue [73]. Another hypothesis for medium-chain TAG effect is their inhibitory effect on apoB synthesis, reducing the VLDL secretion by hepatocytes. This has been observed with octanoate in chicken hepatocytes [74].

Conclusion

We have reported here new knowledge on cellular and physiological functions of the different SFA. For this reason, SFA should no longer be considered as a single group in terms of structure, metabolism, and function.

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