The Fate and Intermediary Metabolism of Stearic Acid

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ABSTRACT: Coming from the Greek for "hard fat," stearic acid represents one of the most abundant FA in the Western diet. Otherwise known as *n*-octadecanoic acid (18:0), stearate is either obtained in the diet or synthesized by the elongation of palmitate, the principal product of the FA synthase system in animal cells. Stearic acid has been shown to be a very poor substrate for TG synthesis, even as compared with other saturated fats such as myristate and palmitate, and in human studies stearic acid has been shown to generate a lower lipemic response than medium-chain saturated FA. Although it has been proposed that this may be due to less efficient absorption of stearic acid in the gut, such findings have not been consistent. Along with palmitate, stearate is the major substrate for the enzyme stearoyl-CoA desaturase, which catalyzes the conversion of stearate to oleate, the preferred substrate for the synthesis of TG and other complex lipids. In mice, targeted disruption of the stearoyl-CoA desaturase-1 (SCD1) gene results in the generation of a lean mouse that is resistant to diet-induced obesity and insulin resistance. SCD1 also has been shown to be a key target of the anorexigenic hormone leptin, thus underscoring the importance of this enzyme, and consequently the cellular stearate-to-oleate ratio, in lipid metabolism and potentially in the treatment of obesity and related disorders.

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STEARATE: STRUCTURE AND SOURCES

Stearate was first described by Michel Eugene Chevreul in 1823 in his studies on fats and oils and is one of the most abundant saturated FA in the Western diet (1). Stearic acid is also denoted as *n*-octadecanoic acid or as 18:0, as it is composed of 18 carbons with no double bonds. Although it is found in small quantities in seed and marine oils, major sources of this long-chain saturated fat include milk fats, which can contain 5 to 15% stearate, as well as lard and cocoa and shea butters, which can contain from 10–35% stearate. Stearic acid is also a large constituent in hydrogenated fats and oils.

Apart from dietary sources, stearate can also be endogenously synthesized from acetyl-CoA molecules (Fig. 1). The biotin-containing acetyl-CoA carboxylase (ACC) catalyzes the irreversible conversion of the two-carbon acetyl-CoA to the three-carbon intermediate, malonyl-CoA. Malonyl-CoA then serves as the precursor for the endogenous synthesis of FA *via* the FA synthase (FAS) multienzyme complex. In bacteria and yeast, FAS exists as seven or two separate polypeptides, respectively, that are tightly associated in one large complex. In mammals, the reactions of the FAS system are catalyzed by individual domains of a single large polypeptide that also includes an acyl carrier protein (ACP) domain (2,3). The large protein functions as a 480 kDa homodimer to carry out seven cycles of sequential condensation, reduction, and dehydration reactions to form the 16-carbon saturated FA, palmitate. Although small amounts of stearate are sometimes formed through the actions of FAS, chain elongation generally stops at 16 carbons, and the palmitate is released from the ACP moiety (2,3). Further elongation generally occurs through the actions of microsomal elongases to form stearate (Fig. 1).

Six different isoforms of FA elongase (Elovl) have been identified in the mouse, rat, and human genomes (3–6). Elov1-1 (Ssc1) and Elovl-6 [LCE, fatty acid elongase (FACE), rElo2] have been shown to elongate saturated and monounsaturated FA (3,7,8). Elovl-2 (Ssc2) acts on 20- to 22-carbon PUFA, whereas Elovl-5 (FAE1, Relo1, Helo1) has a wide range of substrates from 16 to 22 carbons long (7,8). 16:0-CoA has been shown to be a substrate for Elovl-1 and Elovl-6 and is converted to 18:0-CoA by these FA elongases (7–10).

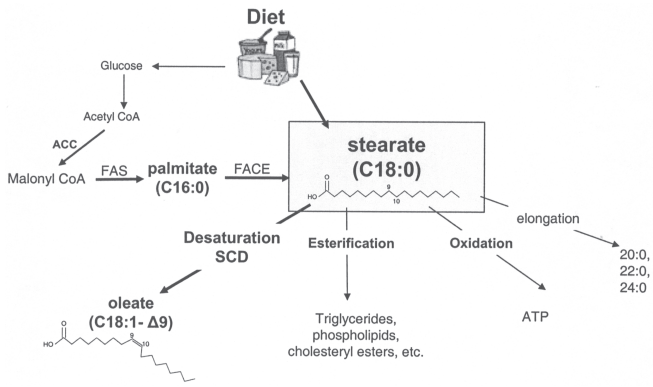

FIG. 1. Synthesis and fate of stearic acid. Stearate can either be obtained from the diet or be synthesized *de novo* in the body through the actions of acetyl-CoA carboxylase (ACC) and the FA synthase (FAS) enzyme complex and through elongation of palmitate by FA elongases (FACE). Once it has been formed, stearate can undergo various fates including further elongation, oxidation, and esterification to form complex lipids or desaturation by the enzyme stearoyl-CoA desaturase (SCD) to form the monounsaturated FA, oleate.

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Abbreviations: ACC, acetyl-CoA carboxylase; ACP, acyl carrier protein; DNL, *de novo* lipogenesis; Elovl, isoforms of fatty acid elongase; FACE, fatty acid-CoA elongase; FAS, fatty acid synthase; LXR, liver X receptor; SCD1, stearoyl-CoA desaturase-1; SRE, sterol response elements; SCAP, SREBP-cleavage activating protein; SREBP, sterol-regulatory element-binding protein.

REGULATION OF STEARATE SYNTHESIS

The pathway of the synthesis of stearate and other FA is highly regulated. The compartmentalization of FA synthesis and oxidation in the cytosol or mitochondria, respectively, allows for reciprocal regulation of these two processes. Also, while the product of FA breakdown is acetyl-CoA, *de novo* synthesis of FA is not a simple reversal of this catabolic process. Instead, the formation of the three-carbon intermediate, malonyl-CoA, is a requisite step in FA synthesis (2). Furthermore, the enzymes involved in the synthesis of stearate are all highly regulated by dietary, hormonal, and physiological changes.

In general, insulin, glucose, 3,5,3′-triiodothyronine, and glucocorticoids have all been shown to induce *de novo* lipogenesis (DNL), whereas long-chain PUFA, epinephrine, and glucagon have been shown to suppress DNL (11–13). There is also considerable evidence for the transcriptional regulation of enzymes of *de novo* FA synthesis, including FAS and Elovl-6 through the actions of the lipogenic transcription factor, sterol-regulatory element-binding protein (SREBP) (3,7,9,10,14).

SREBP are a family of helix-loop-helix transcription factors that were first identified through their ability to bind to a sterol response element found on genes involved in cholesterolgenesis. Three isoforms of SREBP have thus far been identified; SREBP-1a and SREBP-1c regulate genes of lipid synthesis, whereas SREBP-2 has been shown to be involved in cholesterol homeostasis. SREBP-1a and -1c are both transcribed from the same gene locus and differ only at their N-termini; SREBP-2 is encoded by a separate gene. SREBP1c is the major isoform in rodent and human liver and is now recognized as a key regulator of FA and TG synthesis (14,15).

SREBP are initially synthesized as large proteins (125 kDa) anchored to the endoplasmic reticulum membrane with two membrane-spanning domains and with their C-terminal end bound to the SREBP-cleavage activating protein (SCAP). In response to cellular signals such as decreased sterol levels, the SREBP–SCAP complex moves to the Golgi apparatus, where it undergoes two proteolytic events, giving rise to the smaller (65 kDa), mature form of the SREBP protein (14,15). This proteolytic cleavage then results in the transit of the mature form of the protein to the nucleus, where it binds to *cis*-elements termed sterol regulatory elements (SRE) in the promoters of target genes and induces transcription of a variety of genes involved in cholesterol, TG, and FA synthesis; these include ACC and FAS as well as stearoyl-CoA desaturase-1 (SCD1), which converts stearate (18:0) to oleate (18:1n-9) (14–17).

Mice overexpressing SREBP in the liver have been shown to accumulate lipids in their liver as a result of increased expression of lipogenic genes. However, the majority of FA in the livers of these transgenic mice tend to be 18 carbons long rather than 16 carbons long, suggesting that the FA elongase responsible for the synthesis of stearate from palmitate is also upregulated by SREBP (3). Indeed, it was recently shown that Elovl-6, also known as FACE, is upregulated in SREBP transgenic mouse livers (7,10,18). It has since been described that Elovl-6 specifically utilizes 12- to 16-carbon saturated and monounsaturated FA in the liver as substrates. Elovl-6 is also upregulated in leptin-deficient ob/ob mice that have markedly higher hepatic SREBP levels (10). Elovl-6 expression was also shown to be upregulated by agonists of the liver X receptor (LXR) (10), a nuclear receptor that is a strong activator of SREBP-1c transcription.

FATE OF STEARATE

Once stearate has been synthesized in the cell, it can undergo several different fates (Fig. 1) depending on various factors such as the energy charge of the cell, hormonal signals, and so forth. Under conditions of low energy charge, the enzyme carnitine palmitoyl transferase-1 transports stearate to the mitochondria, where it is oxidized (19). Alternately, under conditions of high energy charge, such as after a meal, stearate can be directly esterified to form complex lipids for storage. However, it has been shown that stearate is a very poor substrate for esterification (20). On the other hand, stearate can be desaturated by the actions of the enzyme stearoyl-CoA desaturase to form oleate (18:1n-9), which has been shown to be the preferred substrate for complex lipid synthesis (21). Alternately, stearate can be further elongated to form other long-chain saturated FA (Fig. 1).

DESATURATION: STEAROYL-CoA DESATURASES

In mammalian cells, stearate is rapidly acted on by the enzyme stearoyl-CoA desaturase and is converted to its monounsaturated product, oleate. SCD is the rate-limiting enzyme in the synthesis of monounsaturated FA from their saturated FA precursors. SCD introduces a single double bond between carbons 9 and 10 of the saturated FA and shows high substrate specificity for palmitate and stearate, converting them to palmitoleate and oleate, respectively (21,22).

The genes for SCD have been identified and cloned from several species, including yeast, *Caenorhabditis elegans*, hamster, sheep, rat, mouse, and human. Four different isoforms of the enzyme have been identified in the mouse, whereas two different isoforms have thus far been identified in the human (21,22). In the mouse, SCD1 is the major isoform expressed in white adipose tissue, brown adipose tissue, and the meibomian, Harderian, and preputial glands. It is also dramatically induced in the liver upon high-carbohydrate feeding (21,22). The presence of four different isoforms of SCD in the mouse is partially explained by differential tissue distribution of the various isoforms. However, it is also becoming apparent that these various SCD isoforms may differ in terms of their substrate specificities. It has been suggested, for instance, that although SCD1 and SCD2 may show greater specificity toward the desaturation of stearate (23,24), SCD3 may prefer palmitate as a substrate (25,26). Support for these hypotheses comes from studies using the SCD1 knockout (SCD1−/−) mouse model, which, due to a targeted mutation of the SCD1 gene, exhibits complete loss of SCD1 expression and activity. However, microsomes from the Harderian glands of SCD1−/− mice retain the ability

to desaturate 16:0-CoA, whereas their ability to desaturate 18:0-CoA is reduced by over 90% (21,24). This suggests that SCD1 may prefer stearate over palmitate as a substrate. Studies in the preputial glands of SCD1–/– mice have revealed that although SCD1 and SCD3 activities are virtually absent, SCD2 expression is not attenuated. At the same time, microsomes from the preputial glands of SCD1–/– mice exhibit greater desaturase activity toward 18:0-CoA compared with 16:0-CoA, suggesting that SCD2 prefers stearate as a substrate (21,25). Treatment of SCD1–/– mice with testosterone increases SCD3 expression in preputial glands, concomitantly increasing 16:1n-7 levels; this suggests that the SCD3 isoform may prefer 16:0-CoA as a substrate (21,25). The substrate specificity of the newly identified SCD4, if any, is yet to be determined. These differences in tissue specific expression as well as substrate specificity may provide additional levels of regulation in determining the lipid composition of the cell, thereby regulating diverse cellular processes.

IS STEARATE FUNCTIONALLY DIFFERENT FROM OTHER SATURATED FATS?

In general, saturated fat has been recognized as deleterious to the health because of its hypercholesterolemic and atherogenic effects. Hence, the recommended dietary intake of saturated fat has been set at less than 10% of the total daily fat intake. Because of this generalized recommendation, stearate has been grouped with other saturated FA simply due to its chemical structure. However, there is evidence that the effects of stearate are considerably different from the effects of shorter-chain saturated FA such as laurate, myristate, and palmitate (20,27–31).

The early work of Keys *et al*. (28) and Hegsted *et al*. (29) established that, unlike laurate, myristate, and palmitate, stearate does not raise plasma cholesterol levels. More recently, it has been shown in hamsters that although diets high in laurate, myristate, or palmitate increase plasma cholesterol by depressing LDL receptor activity and increasing the rate of LDL production, stearate does neither and is in fact associated with a hypocholesterolemic response (32). In humans, stearate has been shown to be as potent as oleate at reducing plasma LDL levels (33). Furthermore, our studies with the SCD1–/– mouse have revealed that despite their inability to desaturate stearate into oleate, there is no significant accumulation of stearate in the tissues of SCD1–/– animals even when substantial amounts of stearate are added to their diets (34). Dietary oleate, on the other hand, is able to partially rescue the hypolipidemic profile of SCD1–/– mice (34), suggesting that stearate may not necessarily mediate the hypertriglyceridemic effect associated with saturated FA.

Several hypotheses have been proposed for why stearate may behave differently from its shorter-chain saturated FA counterparts. First, stearate has been shown to be a very poor substrate for TG and cholesteryl ester formation (20,31). It has been suggested that stearate, because of its chain length and saturated nature, is not absorbed efficiently (35). However, studies in humans show that absorption of stearic acid and its metabolizable energy are only marginally lower than those of other FA and are probably insufficient to explain its differential effects on plasma lipoprotein responses (36,37).

It has also been suggested that the effects of stearate may in fact be mediated by its desaturation into oleate, catalyzed by the enzyme SCD (38). Ongoing studies on the role and regulation of SCD will no doubt be key to understanding whether the conversion of stearate to oleate mediates the intracellular effects of stearic acid.

CELLULAR STEARATE-TO-OLEATE RATIOS: CLINICAL IMPLICATIONS

Oleate, the product of SCD, has been shown to be the preferred substrate for the synthesis of TG, cholesteryl esters, and DAG (21). It is abundant in the diet and can be obtained from various sources including animal and vegetable fats. Despite this, the SCD enzyme is subject to various forms of regulation by dietary, hormonal, and environmental factors (22), suggesting an important role for the maintenance of the cellular ratio of stearate to oleate. Indeed, the cellular ratio of oleic to stearic acids has been shown to play a role in various conditions by effecting changes in membrane fluidity and signal transduction that can, in turn, regulate cell growth and differentiation (39–42). In general, changes in SCD expression affect the FA composition of membrane phospholipids, TG, and cholesteryl esters and may thus have an impact on diseases of lipid metabolism including obesity, diabetes, and cardiovascular disease. For instance, murine hypertriglyceridemia has been shown to be well correlated with hepatic SCD activity, and consequently plasma 18:1/18:0 ratios. Furthermore, in human subjects, a low-fat, high-carbohydrate diet was found to cause an increase in the plasma 18:1/18:0 ratio, and this increase was larger in subjects exhibiting a hypertriglyceridemic response to the diet compared with those whose TG levels were lower (43).

More recently, it has also been shown that stearate may also play a role in regulating gene transcription (44). Lin *et al.* (44) have shown that saturated FA, including stearate, are involved in the activation of SREBP, and consequently of lipogenic target genes. This activation requires the transcriptional coactivator PGC-1β and also involves concurrent coactivation of the nuclear receptor LXRα.

Further understanding of the potential role of SCD activity, and therefore of the stearate–oleate ratio in the cell, has come from studies in the SCD1 knockout mouse model, as described in the Desaturation: Stearoyl-CoA Desaturases section. SCD1–/– mice have very low hepatic TG and cholesteryl ester accumulation and decreased whole-body adiposity (45,46). SCD1–/– mice also display decreased lipogenic gene expression as well as increased metabolic rates and lipid oxidation (22,45,47,48). SCD1–/– mice are protected from diet-induced obesity, suggesting that the loss of SCD activity in this mouse model may protect them from hypertriglyceridemia as well as hepatic steatosis (34,47,48). Given the high degree of correlation between atherosclerosis and cardiovascular disease and HDL and LDL ratios, these findings in the SCD1–/– mice are of potential clinical significance.

Furthermore, SCD1−/− mice display greater insulin sensitivity compared with their wild-type littermates and are resistant to diet-induced obesity (49,50). Recently, SCD1 has also been shown to be a downstream target of the anorexigenic hormone leptin (51), suggesting a potentially prominent role for this enzyme in the regulation of appetite and body weight, as well as in insulin sensitivity.

CONCLUSION

As conditions such as obesity reach epidemic proportions, lipid-induced disorders such as hepatic steatosis, hypertriglyceridemia, cardiovascular disease, and insulin resistance have moved to the forefront of public health concerns. Given the severity of this epidemic, there is mounting interest in identifying modifiable risk factors, especially dietary components, that may contribute to the progression or prevention of lipid-induced diseases. Although saturated fats have generally been considered to be prolipogenic and proatherogenic, it seems likely that stearic acid is unique in its effects on plasma lipids as compared with other saturated FA. Stearate is known to be a poor substrate for TG and cholesteryl ester synthesis; this may explain why, unlike laurate, myristate, or palmitate, stearate is generally not associated with a hypercholesterolemic response. Stearate is rapidly converted to oleate by the enzyme SCD, which is subject to various levels of regulation by hormonal, dietary, and physiological factors. Recent studies using the SCD1−/− mouse model have revealed several important aspects of the potential role that the cellular stearate-to-oleate ratio may play in conditions such as obesity and insulin resistance. Further studies will be important in deciphering the specific effects of intracellular stearate in the progression or attenuation of lipid-induced disease.

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