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Review

Regulation of mammalian desaturases by myristic acid: N-terminal myristoylation and other modulations

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ABSTRACT

Myristic acid, the 14-carbon saturated fatty acid (C14:0), usually accounts for small amounts (0.5%–1% weight of total fatty acids) in animal tissues. Since it is a relatively rare molecule in the cells, the specific properties and functional roles of myristic acid have not been fully studied and described. Like other dietary saturated fatty acids (palmitic acid, lauric acid), this fatty acid is usually associated with negative consequences for human health. Indeed, in industrialized countries, its excessive consumption correlates with an increase in plasma cholesterol and mortality due to cardiovascular diseases. Nevertheless, one feature of myristoyl-CoA is its ability to be covalently linked to the N-terminal glycine residue of eukaryotic and viral proteins. This reaction is called N-terminal myristoylation. Through the myristoylation of hundreds of substrate proteins, myristic acid can activate many physiological pathways. This review deals with these potentially activated pathways. It focuses on the following emerging findings on the biological ability of myristic acid to regulate the activity of mammalian desaturases: (i) recent findings have described it as a regulator of the Δ4-desaturation of dihydroceramide to ceramide; (ii) studies have demonstrated that it is an activator of the Δ6-desaturation of polyunsaturated fatty acids; and (iii) myristic acid itself is a substrate of some fatty acid desaturases. This article discusses several topics, such as the myristoylation of the dihydroceramide Δ4-desaturase, the myristoylation of the NADH-cytochrome b5 reductase which is part of the whole desaturase complex, and other putative mechanisms.

1. Introduction

Myristic acid, the 14-carbon saturated fatty acid (C14:0), usually accounts for small amounts (less than 1% weight) of total fatty acids in animal tissues [1] but is more abundant in milk fat (7%–12% of total fatty acids) or in copra and palmist oils (15%–20% of total fatty acids). Dietary saturated fatty acids (SFA) are usually thought to have negative consequences for human health. Indeed, high intake (more than 15% of daily energy intake) of SFA is positively associated with increased levels of blood cholesterol and high coronary heart disease mortality rates. According to this negative assumption, SFA are often still considered as a single group even though it is now well-known that they do not have similar levels in common foods: palmitic acid and stearic acid are universally found in natural fats whereas myristic acid is specifically found in milk fat. Moreover, SFA do not have similar metabolic fates [2,3], and each SFA possess specific functions [4]. Among SFA, some recent findings strongly suggest that myristic acid (C14:0) may have new important and specific regulatory roles in the cell because it is able to modify many enzyme activities or protein functions through their N-terminal myristoylation. Myristic acid is indeed directly and specifically involved in protein N-terminal myristoylation [5] (Fig. 1), that refers to the highly specific covalent attachment of myristic acid by an amide linkage to the NH_2-terminal glycine residue of an increasing number of eukaryotic and viral proteins [6]. Myristoyl-CoA: protein N-myristoyltransferase (NMT, EC 2.3.1.97), the enzyme catalyzing this stable acylation, has been identified in many organisms [7–10]. In mammals, two distinct NMT genes referred to as type 1 and 2 [8] have been described. Knocking down NMT1 is lethal in mice [11]. 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 [6,12]. Through this covalent modification of proteins, myristoyl-CoA coming from the activation of myristic acid by acyl-CoA synthetases therefore exhibits a specific and important role in modulating protein functions.

Among the enzymes involved in lipid biosynthesis and metabolism, desaturases have always been presented as crucial and rate-limiting steps in the metabolic pathways [13]. Throughout the past years, we have noticed that several members of the mammalian

Abbreviations: DES, dihydroceramide Δ4-desaturase; FADS, fatty acid desaturase; NCb5R, NADH-cytochrome b5 reductase; NMT, myristoyl-CoA: protein N-myristoyl-transferase; PUFA, polyunsaturated fatty acids; SCD, stearoyl-CoA desaturase; SFA, saturated fatty acids

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family of membrane-bound desaturases possess a potential site of myristoylation (Fig. 2). Indeed, not only protein sequences deduced from mammalian FADS2 (fatty acid desaturase 2, Δ6-desaturase) [14–16] and FADS3 (fatty acid desaturase 3, putative desaturase) [17–19] but also DES1 and DES2 (two isoforms of dihydroceramide Δ4-desaturase, DES) [20–22] genes exhibited the presence of an N-terminal glycine residue [23]. These proteins also share the three characteristic histidine boxes [21], which are associated with the ability of these enzymes to introduce a cis- or trans-double bond in the carbon chain of lipid substrates (fatty acids or sphingolipids) (Fig. 2). Moreover, all these desaturases are believed to cooperate with both cytochrome b5 and NADH-cytochrome b5 reductase (NCb5R) in the endoplasmic reticulum membrane [24,25] (Fig. 3). This model was first proposed for the stearoyl-CoA desaturase (SCD or Δ9-desaturase) [26,27]. Interestingly, studies have demonstrated that NCb5R is one of the N-terminally myristoylated proteins [28–30]. The hypothesis therefore put forward suggests that the myristoylation of this protein, which is part of the whole complex of desaturation, can participate in the myristic acid associated-regulation of desaturases family members (Fig. 3).

In this context, this review will focus on the following emerging findings on the biological ability of myristic acid to regulate the activity of mammalian desaturases: (i) recent findings have described it as a regulator of the Δ4-desaturation of dihydroceramide to ceramide through the N-myristoylation of the dihydroceramide Δ4-desaturase; (ii) studies have demonstrated that it is an activator of the Δ6-desaturation of polyunsaturated fatty acids, and several molecular mechanisms have been proposed including N-myristoylation of the NADH-cytochrome b5 reductase; and (iii) myristic acid itself is also a substrate of some desaturases.

2. Myristic acid activates dihydroceramide Δ4-desaturase 1 through its N-terminal myristoylation

We were interested in dihydroceramide Δ4-desaturase (DES) because both DES1 and DES2 isoforms present a potential site of myristoylation (Fig. 2). These two different isoforms of dihydroceramide Δ4-desaturases (DES1 and DES2) have been identified in mice, rats, and humans [20–22]. The regulation of these enzymes is not yet

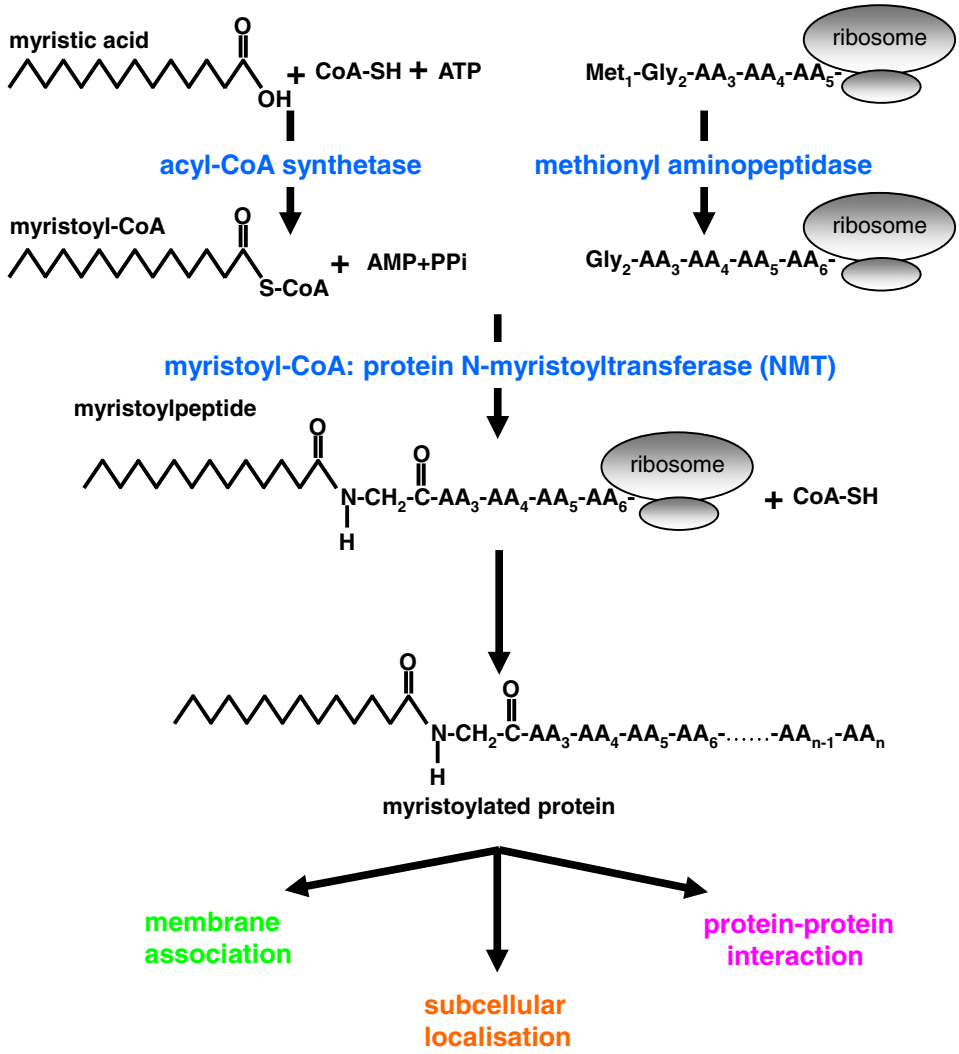

Fig. 1. N-terminal myristoylation of a protein, during its translation, by myristoyl-CoA: protein N-myristoyltransferase (NMT) and biological consequences for the myristoylated proteins. Myristic acid is activated to myristoyl-CoA by the acyl-CoA synthetase. During the translation of the protein, methionyl aminopeptidase removes the initial methionine residue, and a glycine residue appears at the N-terminal end. Myristoyl-CoA: protein N-myristoyltransferase catalyzes the formation of the amide bond between the 2 co-substrates. Typically a co-translational modification, post-translational N-myristoylation of specific proteins has also been shown to occur after the cleavage by caspases which results in the exposition of an internal glycine residue [65].