Biochimie 120 (2016) 40–48

Contents lists available at ScienceDirect

Biochimie

journal homepage: www.elsevier.com/locate/biochi

Review

Revisiting the metabolism and physiological functions of caprylic acid (C8:0) with special focus on ghrelin octanoylation

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ARTICLE INFO

Article history:
Received 9 March 2015
Accepted 1 August 2015
Available online 4 August 2015

Keywords:
Medium-chain saturated fatty acids
Caprylic acid
Octanoic acid
Octanoate
Metabolism
Ghrelin octanoylation
Acylation

ABSTRACT

Caprylic acid (octanoic acid, C8:0) belongs to the class of medium-chain saturated fatty acids (MCFAs). Dairy products and specific oils like coconut oil are natural sources of dietary C8:0 but higher intakes of this fatty acid can be provided with MCT (Medium-Chain Triglycerides) oil that consists in 75% of C8:0. MCFAs have physical and metabolic properties that are distinct from those of long-chain saturated fatty acids (LCFAs ≥ 12 carbons). Beneficial physiological effects of dietary C8:0 have been studied for a long time and MCT oil has been used as a special energy source for patients suffering from pancreatic insufficiency, impaired lymphatic chylomicron transport and fat malabsorption. More recently, caprylic acid was also shown to acylate ghrelin, the only known peptide hormone with an orexigenic effect. Through its covalent binding to the ghrelin peptide, caprylic acid exhibits an emerging and specific role in modulating physiological functions themselves regulated by octanoylated ghrelin. Dietary caprylic acid is therefore now suspected to provide the ghrelin O-acyltransferase (GOAT) enzyme with octanoyl-CoA co-substrates necessary for the acyl modification of ghrelin. This review tries to highlight the discrepancy between the formerly described beneficial effects of dietary MCFAs on body weight loss and the C8:0 newly reported effect on appetite stimulation *via* ghrelin octanoylation. The subsequent aim of this review is to demonstrate the relevance of carrying out further studies to better understand the physiological functions of this particular fatty acid.

Contents

Abbreviations: FFA, free fatty acid; GH, growth hormone; GOAT, ghrelin O-acyltransferase; GHSR-1a, growth hormone secretagogue receptor 1a; LCFA, long-chain fatty acid; LCT, long-chain triglyceride; MCFA, medium-chain fatty acid; MCT, medium-chain triglyceride; PUFA, polyunsaturated fatty acid; TG, triglyceride.

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http://dx.doi.org/10.1016/j.biochi.2015.08.002
0300-9084/

1. Introduction

Caprylic acid (octanoic acid, C8:0) belongs to the class of medium-chain saturated fatty acids (MCFAs) which also includes caproic acid (C6:0) and capric acid (C10:0). MCFAs are characteristic nutrients present in dairy products [1] and in specific oils like palm kernel and coconut oils [2]. They display physical and metabolic properties that are distinct from those of long-chain saturated fatty acids (LCFAs ≥12 carbons), leading to their rapid gastro-intestinal hydrolysis and absorption, specific transport through the portal vein and rapid beta-oxidation in the liver [3]. In the past, these metabolic specificities leading to a high catabolism and low tissue storage [4] have been associated with beneficial or neutral physiological effects of dietary MCFAs, compared with LCFAs. More recently, the discovery of stomach ghrelin as the endogenous ligand of growth hormone secretagogue receptor 1a (GHSR-1a) [5] and the description of its essential and unique post-translational octanoylation catalyzed by the ghrelin O-acyltransferase (GOAT) [6,7] has added a new level of complexity in the understanding of the physiological functions regulated by dietary C8:0.

In the present review, we therefore revisit the knowledge on this fatty acid (FA), focusing on the discrepancy between the historically described beneficial effects of dietary MCFAs (including C8:0) on body weight and fat loss and its newly reported effect on food consumption and appetite stimulation *via* ghrelin octanoylation.

2. Food sources and biosynthesis of caprylic acid in animals

Natural food sources of caprylic acid are restricted to specific vegetable oils and milk products. Caprylic acid is abundant in coconut oil (6–10% of FAs, with C8:0 mainly in sn-1 and -3 positions on the triglycerides, TG) and in palm kernel oil (2–5% of FAs) [8]. These two edible oils are also characterized by high amounts of capric acid (5–10% and 3–5% of FAs, respectively) and lauric acid (39–54% and 44–51% of FAs). Milk is the only natural source of animal caprylic acid with strong differences between mammalian species. C8:0 represents about 0.5% of FAs in human milk [9], but is higher in cow milk (1–2%) [1], in goat milk (3%) [10], in rat milk (5–6%) [11] and reaches up to 15–18% in rabbit milk [12]. Caprylic acid and other MCFAs are primarily esterified in sn-3 position of the TGs in cow [1], rat [13] and human [9] milks.

De novo synthesis of short to medium chain saturated FAs (C4:0 to C10:0) in the mammary gland of ruminant species, catalyzed by the thioesterase I included in the Fatty Acid Synthase (FAS) complex and leading to their presence in ruminant milk, has been well documented [14]. In the lactating mammary gland of non-ruminant mammalian species, the presence of a cytosolic thioesterase II [15], independent of the FAS complex, explains the synthesis of saturated FAs (SFAs) with 6–14 carbons. Peroxisomal beta-oxidation leading to chain-shortening of C16:0 to C14:0 has also been described in hepatocytes [16]. However, such a mechanism leading to the endogenous synthesis of C8:0 has not been described in animal tissues.

In western diets, total MCFAs represent therefore less than 2% of dietary energy with caprylic acid being predominantly provided by milk fat. The dietary level of caprylic acid and other MCFAs may be higher in some Asian countries consuming coconut or palm kernel oils [2]. The Medium Chain Triglyceride (MCT) oil, produced from coconut oil and made up with 75–80% of C8:0, can be consumed to increase the intake of dietary C8:0. MCT oil is currently used for clinical purposes only, in oral or enteral nutrition when the digestion, absorption or transport of Long Chain Triglycerides (LCT) is impaired, or in parenteral nutrition when rapid energy supply is needed. Diets highly enriched with MCT (40–60% of energy) have also been used as an alternative to ketogenic diets for the potential treatment of neurological disorders [17].

3. Digestion and absorption of dietary lipids containing caprylic acid

The digestion of dietary fat is a complex and dynamic process which starts in the upper gastrointestinal tract under the action of preduodenal lipase (gastric lipase in humans or its homologous lingual lipase in rats [11]) and is completed in the small intestine by pancreatic lipase (Fig. 1). Although the existence and functional importance of a preduodenal lipase has been disputed in the past [18], it is now described as contributing to 15–20 % of the whole lipolysis process [19]. Preduodenal lipase is described as playing two important roles: first, in driving the early release of short and medium chain SFAs, including caprylic acid, secondly in triggering the subsequent action of pancreatic lipase [20]. Part of MCFAs coming from dietary MCTs or milk TGs may therefore be directly absorbed by the stomach mucosa [12], as shown by studies using radiolabelled lipids administered to suckling rats [21,22]. However, the amounts of FAs involved in this gastric absorption, the mechanism of absorption (which could be a simple diffusion) [21] and the subsequent gastric metabolic fate of these MCFAs still haven't been clearly described [12,23]. They may depend on physiological parameters such as age (neonates vs. adult). Since gastric lipase shows a stereo-preference for the hydrolysis of ester bonds at the sn-3 position of TGs [24], this process is particularly adapted in the context of dairy fat digestion [23], to release the MCFAs located predominantly at this position [13].

Then, MCFAs which have escaped the absorption at the gastric level are absorbed by small intestinal cells, like LCFAs, after the subsequent action of duodenal pancreatic lipase on both dietary remaining MCTs and LCTs (Fig. 1). However, unlike LCFAs which are re-esterified with 2-monoglycerides into TGs in enterocytes and incorporated into chylomicrons which then enter the lymphatic system, MCFAs are directly transferred to the portal circulation and transported as free fatty acids (FFAs) with albumin to the liver [25].

4. Cellular metabolism of caprylic acid

Dietary MCFAs coming from the portal circulation are directly taken up by the liver and rapidly subjected to mitochondrial beta-oxidation [26], since they easily enter the mitochondria independently of the carnitine transport system, as opposed to LCFAs [27]. Once inside the liver mitochondria, MCFAs are activated by medium-chain acyl CoA synthetases [28], forming CoA derivatives which are catabolized. In addition to the mitochondrial beta-oxidation, peroxisomal beta-oxidation may participate in their overall oxidation process even if LCFAs are more subjected to this pathways [29]. Omega-oxidation of MCFAs may occur in the endoplasmic reticulum (ER) and in the cytoplasm when the mitochondrial beta-oxidation is exceeded, leading to the synthesis of dicarboxylic acids [30]. Conversely, the potential use of dietary C8:0 for glycerolipid esterification appears very limited [27], except in hepatocytes isolated from rabbits at birth [31], which disappears in older rabbit. In hepatocytes isolated from adult rats initially fed with a low-fat diet or high-fat diets composed of MCTs or LCTs, the rates of [1–^{14}C]-caprylic acid oxidation was similarly high [32]. Even when administered intravenously and not orally in rats, radiolabeled tricaprylin led to a high incorporation of radioactivity (90% after 24 h) in expired CO_2 and poor radioactive incorporation into cellular lipids [33]. In some cases, depending on the amount of dietary MCFAs and the duration of the diet, the high level of hepatic beta-oxidation may lead to an acetyl-CoA concentration exceeding the Krebs cycle capacity. In these cases, acetyl-CoA is known to be directed