

Special milk lipids improve health

Fortifying milk fat with medium- and short-chain fatty acids by distillation improves metabolic health

Most of the fat in milk is comprised of triacylglycerol, a glycerol molecule to which three fatty acids are esterified. Milk fat comprises a large variety of fatty acids, and the diversity of triacylglycerol species is great. The typical fatty acids in milk, as in the typical Danish diet, are long-chain fatty acids (LCFAs), most often consisting of a chain length of 16-18 carbon atoms. Medium-chain fatty acids (MCFAs) refer to fatty acids, which consist of 8-12 carbon atoms. MCFAs make up ~10% of the total fat in milk. Milk is a unique dietary source of MCFAs, as only less common food items such as coconut oil and palm kernel oil contain significant quantities of MCFAs. Interestingly, the presence of MCFAs in infant milk is greatly conserved between humans and across animal species, indicating their importance to infant development.

Health benefits of MCFA

Intake of MCFAs is shown in previous experiments to improve insulin sensitivity and energy metabolism in humans. In this line, we have shown that dietary replacement of only 30 g LCFAs by MCFAs prevented development of insulin resistance during three days of overfeeding in humans.

In our recently finalized project, we were able to further demonstrate that the intake of just 35 g of these MCFAs led to postprandial lowering of blood glucose levels and increased energy expenditure, while also avoiding an increase in circulating triacylglycerol levels observed when ingesting the same amount of LCFAs. Interestingly, these attractive metabolic effects of MCFA intake were present even in metabolically compromised individuals with obesity and sustained after daily supplementation for 8 days. This implies that daily intake of MCFAs could be a potential dietary dairy-derived tool improving blood sugar levels and body weight regulation and countering dyslipidemia both in healthy individuals and metabolically compromised individuals with obesity.

While we found that the blood glucose regulatory effects of MCFAs appeared related to a noteworthy activation of pancreatic re-

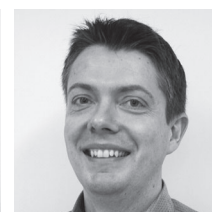
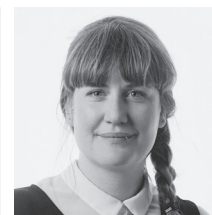
lease of insulin, intake of MCFAs was also accompanied by a very potent release of signaling metabolites from the liver, so-called ketone bodies, that have been associated with several beneficial metabolic effects and thought to mediate positive effects of fasting and ketogenic diet intake.

Molecular mechanisms underlying effects of MCFAs

Unlike the more abundant LCFAs, which enter the blood via the lymphatic system as triacylglycerols packaged into lipid-carrying particles, MCFAs are directly absorbed from the intestine into the portal vein to the liver, where they are metabolized. Therefore, we speculated that some of the observed beneficial metabolic effects of dietary MCFAs on a whole-body level were mediated by release of signaling molecules from the liver. Consequently, we administered MCFAs to mice, and by subsequent use of sophisticated global molecular biology screening tools we were able to identify two signaling molecules, GDF15 and FGF21, that were produced in the liver in response to MCFA intake and increased in the circulation after intake. By taking advantage of transgenic mice lacking functional GDF15 and FGF21 signaling, we further demonstrated that these two hormones were necessary for the full effect of MCFAs in mediating satiety and lowering of liver lipid levels, suggesting that these metabolic health effects appeared driven by induction of hepatic GDF15 and FGF21 release upon MCFA intake in mice. Collectively, these novel findings have made it possible to unravel a part of the molecular biology underlying the metabolic effects of MCFA intake, providing insights into how these lipids orchestrate physiological effects.

Methodology enriching MCFAs content of milk fat

Excited by our findings of MCFA-mediated health effects, we urged to exploit this knowledge for application in a dietary dairy context. While cow milk fat contains MCFAs in a balanced mix but in relatively low con-



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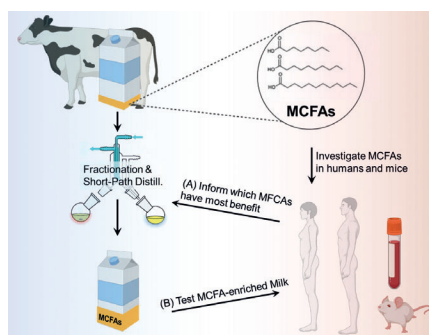
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centrations, enriching them could amplify health benefits of dairy products. While fractionation of milk fat today is mostly done for obtaining improved textural functionalities of the fat, we here targeted the composition of the fat fraction to obtain specific health benefits. By selecting cow milk with the highest MCFA content and using a heating technique called short-path distillation (SPD) we were able to produce milk fat with much higher content of MCFAs than raw milk. We developed a volatility-based workflow to produce milk fat with a 2-fold enrichment of MCFAs (from 10.1 to 20.2% compared to native milk fat). This was a marked improvement compared with previous attempts to increase the MCFA content of milk fat from feeding cows specific diets. Interestingly, by doing SPD of the milk fat we also enriched with short-chain fatty acids (SCFAs; 4-6 carbon atoms) increasing the amount from 6.9% to 15% and also enriched the amount of vitamin E (47-63 mg/100g fat compared to 2.5 mg/100g in milk fat). We further experienced that combining SPD with prior dry or solvent fractionation did not lead to significant enrichment of MCFAs. Using milk fat from Jersey cows yielded slightly higher MCFA content in the distillate (MCFA-enriched milk fat). Unfortunately, the distillate after SPD represented approximately only 8-12% of the starting material (milk fat). We therefore also investigated the functionality of the rest material (side-stream occupying ~90% of the mass – so-called “retentate”) to ensure that the practice did not create a dysfunctional side product making the strategy unsustainable in potential future commercial large-scale production. Comfortingly, while the retentate was expectedly enriched in LCFAs and reduced in SCFAs and MCFAs compared to milk fat, we established that the retentate stream had similar functionality and stability



as anhydrous milk fat. SPD appears hence usable as sustainable milk fat distillation strategy to optimize the health of dairy products in future industrial settings without creating a dysfunctional rest product.

Health effects of milk fat enriched with MCFAs

To investigate actual functional health effects of intake of SPD-derived MCFA-enriched milk fat, we performed proof-of-concept studies in mice and humans. Excitingly, we demonstrated that acute administration of this fortified milk fat increased circulating ketone bodies, reduced blood glucose levels, and suppressed food intake in mice. In humans, acute ingestion resulted in increased circulating ketone bodies, trended to attenuate postprandial blood glucose levels, and acutely elevated energy expenditure. Together, these findings showed that milk products enriched with SCFAs- and MCFAs may hold significant metabolic advantages.

Industrial benefits

In our project, we combined state-of-the-art technology and biology to create a new dairy product that has the potential to become a nutritional tool to help combat obesity, type 2 diabetes, and metabolic syndrome. Such functional foods are in high demand by consum-

ers. Moreover, the project led to optimization of processes related to milk fractionation and distillation. Thus, the present project provides new technology to enrich MCFAs in milk fat and demonstrates that milk products enriched with MCFAs appear to hold significant metabolic advantages and have the potential to increase the value of milk fat products by introducing new scalable processing technologies. This opens exciting avenues for the dairy industry. By elucidating novel metabolic effects of MCFA intake and involved underlying physiological and molecular mechanisms uncovering mode-of-action for the health benefits of MCFAs, we further created potential for changing the dietary guidelines and provide novel pharmaceutical targets for metabolic disease prevention and/or treatment. Interestingly since we thoroughly investigated the retentate (side stream) from the present SPD technology and show that it has similar functionality as native milk, and thereby is expected to be able to be used as ingredients like native milk fat, we further believe we have found a technology that can be used to enrich milk fat to improve health and at the same time in a sustainable way be able to use the rest products from the production to further commercial and relevant consumable actions. ●



PROJECT OVERVIEW

Title: SMIL – Special Milk Lipids for Health.

Project manager: Professor Bente Kiens, Department of Nutrition, Exercise and Sports, University of Copenhagen.

Participants: Aarhus University, University of Copenhagen, and Arla Foods for Health.

Project period: January 2021 to December 2024.

Objective: Medium-chain fatty acids have been shown to lower body weight and improve the metabolic syndrome. We want to create a novel dairy ingredient rich in medium fatty acids and assess its potential health benefits, while also identifying mechanisms and biomarkers for medium chain fatty acid action.

Funding: Milk Levy Fund, Arla Foods for Health, and the Novo Nordisk Foundation.

PROJECTS RELATED TO
THE DANISH DAIRY RESEARCH FOUNDATION

ABSTRACT

Milk fat has traditionally been accused of being harmful for metabolic health and body weight regulation. However, our recent collaborative research project between researchers at University of Copenhagen and Aarhus University – funded by the Milk Levy Fund, Arla Food for Health and the Novo Nordisk Foundation - reveals health beneficial effects of unique fatty acids present in milk and elucidates their underlying physiology and biological function at a molecular level. Furthermore, we have developed a methodology to enrich milk fat with these specific fatty acids, and proof-of-concept studies with such fortified milk fat demonstrate promising metabolic effects in both rodents and humans.