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Journal of Nutritional Biochemistry 26 (2015) 1136–1146

Journal of Nutritional Biochemistry

Human, donkey and cow milk differently affects energy efficiency and inflammatory state by modulating mitochondrial function and gut microbiota☆

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Received 3 October 2014; received in revised form 7 May 2015; accepted 7 May 2015

Abstract

Different nutritional components are able, by modulating mitochondrial function and gut microbiota composition, to influence body composition, metabolic homeostasis and inflammatory state. In this study, we aimed to evaluate the effects produced by the supplementation of different milks on energy balance, inflammatory state, oxidative stress and antioxidant/detoxifying enzyme activities and to investigate the role of the mitochondrial efficiency and the gut microbiota in the regulation of metabolic functions in an animal model. We compared the intake of human milk, gold standard for infant nutrition, with equicaloric supplementation of donkey milk, the best substitute for newborns due to its nutritional properties, and cow milk, the primary marketed product. The results showed a hypolipidemic effect produced by donkey and human milk intake in parallel with enhanced mitochondrial activity/proton leakage. Reduced mitochondrial energy efficiency and proinflammatory signals (tumor necrosis factor α, interleukin-1 and lipopolysaccharide levels) were associated with a significant increase of antioxidants (total thiols) and detoxifying enzyme activities (glutathione-*S*-transferase, NADH quinone oxidoreductase) in donkey- and human milk-treated animals. The beneficial effects were attributable, at least in part, to the activation of the nuclear factor erythroid-2-related factor-2 pathway. Moreover, the metabolic benefits induced by human and donkey milk may be related to the modulation of gut microbiota. In fact, milk treatments uniquely affected the proportions of bacterial phyla and genera, and we hypothesized that the increased concentration of fecal butyrate in human and donkey milk-treated rats was related to the improved lipid and glucose metabolism and detoxifying activities.
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Keywords: Mitochondria; Microbiota; Milk; Redox-status; SCFAs

1. Introduction

Evidence from animal and human studies indicates that mitochondrial function and gut microbiota influence metabolic homeostasis.

Mitochondria play a central role in cellular function and metabolism by coupling cellular respiration to the production of ATP. However, this coupling is not perfectly tight. Approximately 20% of the standard metabolic rate in mammals is due to a leak of protons across the mitochondrial inner membrane (basal proton leak) in a manner that uncouples cellular respiration from ATP production, thereby generating heat [1]. In addition to this basal leak, there is an inducible leak of protons catalyzed by free fatty acids (FFAs) [2]. Recent work suggests that an inducible proton leak might have an important role in the protection against reactive oxygen species (ROS) [3]. Moreover, mitochondria play a key role in cell signaling through production of ROS that modulate redox signaling. Nuclear factor E2-related factor-2 (Nrf2) is a transcription factor that orchestrates the expression of battery of antioxidant and detoxification genes under both basal and stress condition [4]. Nrf2 also modulates genes involved in metabolic

Abbreviations: ALT, alanine aminotransferase; CM, cow milk; CPT, carnitine-palmitoyl-transferase; DM, donkey milk; FFA, free fatty acid; GSH, glutathione; GSSG, glutathione disulfide; GST, glutathione-*S*-transferase; HM, human milk; HOMA, homeostasis model assessment; IL-1, interleukin-1; IL-10, interleukin-10; LPS, lipopolysaccharide; MCP-1, monocyte chemoattractant protein-1; NQO1, NAD(P)H:Quinone Oxidoreductase; Nrf2, nuclear factor erythroid-2-related factor-2; OTUs, operational taxonomic units; RCR, respiratory control ratio; ROS, reactive oxygen species; SCFAs, short-chain fatty acids; TNF-α, tumor necrosis factor α; UCP2, uncoupling protein-2.

☆ Grants: This work was supported by grants from the FNRS and PDR (projet de recherche, Belgium) and ERC Starting Grant 2013 (European Research Council, Starting Grant 336452-ENIGMO).

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http://dx.doi.org/10.1016/j.jnutbio.2015.05.003
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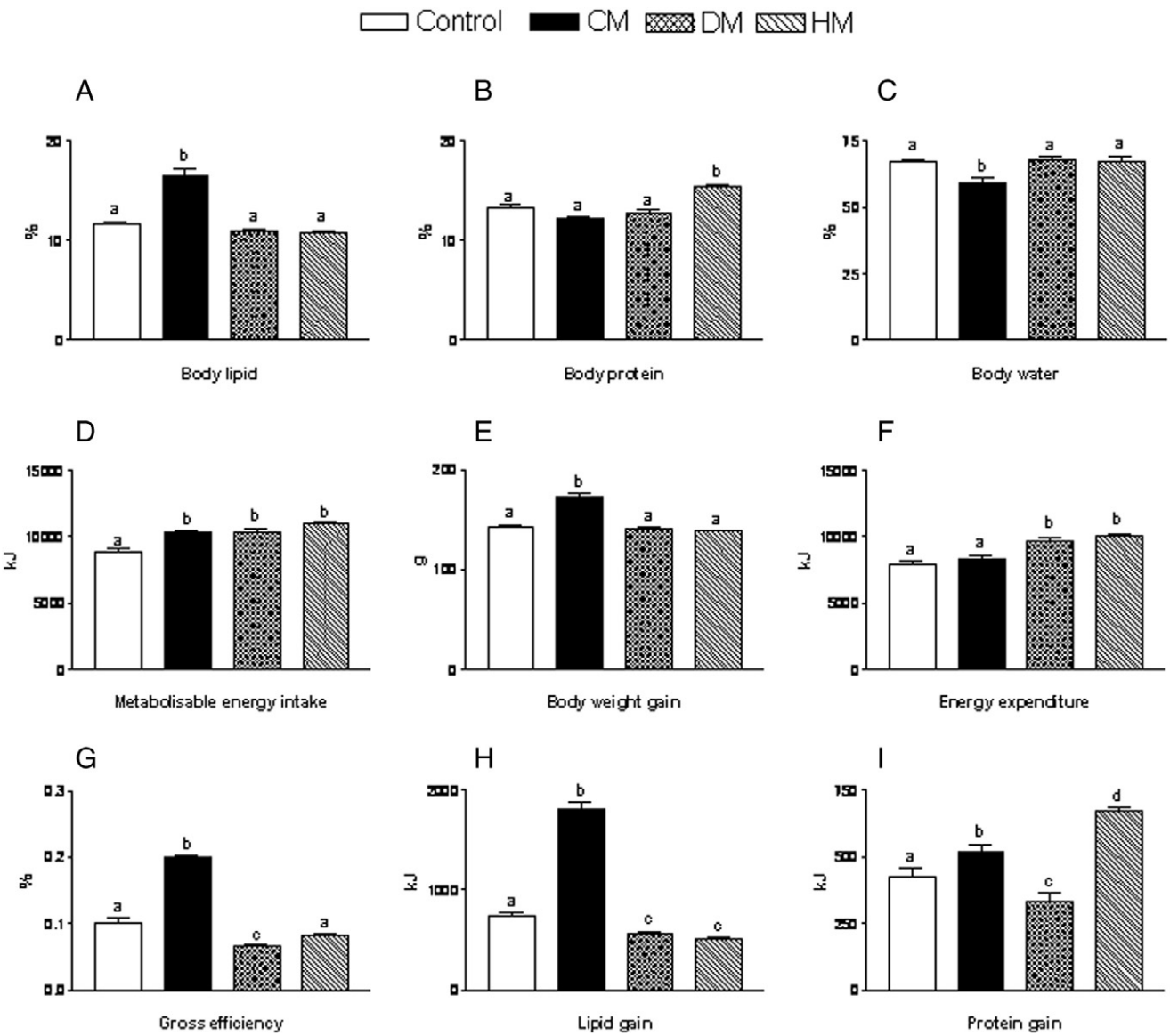

Fig. 1. Body composition and energy balance. Body lipid (A), body protein (B), body water content (C), metabolisable energy intake (D), body weight gain (E), energy expenditure (F), gross efficiency (G), lipid gain (H) and protein gain (I) were reported. The results are expressed as the means±S.E. from $n=7$ animals/group. Different superscripted letters indicate statistically significant differences ($P<.05$).

regulation, such as fibroblast growth factor 21 (FGF21), a liver-derived pro-lipolytic hormone and peroxisome proliferator-activated receptors (PPARs), which play an important role in nutrient homeostasis [5]. Notably, the link between metabolism, ROS homeostasis and mitochondrial metabolism is further indicated by the role played by PPARγ coactivators-1 (PGC-1). Among them, PGC-1α plays an important role in mitochondrial biogenesis and in the regulation of genes responsible for ROS detoxification [6], while PGC-1β is involved in mitochondrial metabolism and its activation exerted a protective effects from lipid overload [7].

Animal and human studies indicate that the metabolic function develops primarily after birth when the newborn is first exposed to nutrition via the gastrointestinal tract and that the composition of the gut microbiota influences body composition, digestion and metabolic homeostasis [8,9].

Phylogenic changes in gut microbiota composition and the production of bacterial metabolites, including short-chain fatty acids (SCFAs), can interact with reach host tissues to act as metabolic regulators and to control energy metabolism and inflammatory state [10].

Therefore, nutritional strategies are able, by influencing the mitochondrial function [11,12] and microbiota composition, to favor the appropriate development of metabolic and immune system functions, and this strategy is now considered a feasible means to prevent diseases such as obesity, diabetes and allergies [8,9].

Table 1
Serum parameters

	Control	CM	DM	HM
Glucose (mg/dl)	138.6±2.1[a]	130.1±5.7[a]	112.1±2.7[b]	112.7±3.7[b]
Insulin (μg/l)	0.273±0.018[a]	0.274±0.019[a]	0.271±0.019[a]	0.201±0.013[b]
HOMA index	2.19±0.12[a]	2.09±0.13[a]	1.75±0.12[b]	1.314±0.10[c]
Triglycerides (mg/dl)	116±5.3[a]	132±7.5[a]	90±4.1[b]	120±5.2[a]
Total cholesterol (mg/dl)	61±1.6[a]	63±1.1[a]	58±1.2[a]	59±1.5[a]
ALT (U/l)	67±2.0[a]	71±3.2[a]	62±2.0[a]	44±2.6[b]

Data are the means ± S.E. Data with different superscripted letters are significantly different ($P<.05$).

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