Molecular and Cellular Endocrinology xxx (2017) 1–5

Contents lists available at ScienceDirect

Molecular and Cellular Endocrinology

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

"With a little help from my friends" - The role of microbiota in thyroid hormone metabolism and enterohepatic recycling

Camilla Virili [a, b], Marco Centanni [a, b, *]

[a] Department of Medico-Surgical Sciences and Biotechnologies, "Sapienza" University of Rome, Corso Della Repubblica 79, 04100 Latina, Italy
[b] Endocrinology Unit, AUSL Latina, Corso Della Repubblica 79, 04100 Latina, Italy

ARTICLE INFO

Article history:
Received 18 October 2016
Received in revised form
28 January 2017
Accepted 31 January 2017
Available online xxx

Keywords:
Microbiota
Iodothyronines metabolism
Levothyroxine
Enterohepatic circulation
Thyroxine malabsorption
Selenium

ABSTRACT

The gut microbiota is composed of over 1200 species of anaerobes and aerobes bacteria along with bacteriophages, viruses and fungal species. Increasing evidence indicates that the intestinal microbiota, beside digestive equilibrium, is also crucial for immunologic, hormonal and metabolic homeostasis. The intestinal microbiota interacts with distant organs by signals which may be part of the bacteria themselves or their metabolites. Dysbiosis has been observed in inflammatory or autoimmune disorders such as multiple sclerosis or type 1 diabetes as well as in obesity and type 2 diabetes. Functional thyroid disorders were associated with bacterial overgrowth and a different microbial composition. Although thyroid metabolism was apparently disregarded, the interference of microbiota on peripheral iodothyronine homeostasis is an intriguing issue. In this review we focused on the interactions of intestinal microbiota with thyroid-related micronutrients and with the metabolic steps of endogenous and exogenous iodothyronines.

1. Introduction

The gut microbiota is composed of over 1200 species of anaerobes and aerobes bacteria along with bacteriophages, viruses and fungal species (Schroeder and Bäckhed, 2016). Human beings host different sets of bacteria in their gut, amassing some 160 species for each individual (Qin et al., 2010). They constitute a mass of approximately 1.5–2 kg, in which strictly anaerobic bacteria are the most represented (Qin et al., 2010). This huge community of bacteria is essentially composed of Bacterioidetes, Firmicutes, Actinobacteria, Proteobacteria and Verrucomicrobia, all phyla asymmetrically distributed in the gut in an increasing fashion from the stomach to the colon. Early in life, genetic background and environmental factors contribute to shaping the host microbial composition. It has been hypothesized that each individual may be clustered in 3 main enterotypes based on the relative distribution of the genera Ruminococcus, Bacteroides and Prevotella (Arumugam et al., 2011)

Individual gut microbial composition becomes more complex with increasing age, and in adult life its substantial stability may be transiently perturbed (dysbiosis) by long term diet changes, drug interference and regional or systemic pathologic conditions (Montalto et al., 2009). Host microbiota is crucial not only for digestive equilibrium but also immunologic, hormonal and metabolic homeostasis (Shanahan, 2011). The intestinal microbiota interacts with distant organs by signals that may be part of the bacteria themselves or their metabolites (Schroeder and Bäckhed, 2016). Dysbiosis has been observed in inflammatory or autoimmune disorders such as multiple sclerosis, type 1 diabetes, inflammatory bowel and rheumatic diseases, as well as in dysmetabolic disorders such as obesity and type 2 diabetes (Tlaskalovà-Hogenovà et al., 2011). A symptomatic small intestinal bacterial overgrowth, reversed by antibiotic treatment, has been described in hypothyroidism and it has been suggested that bacterial excess was responsible for changes in neuromuscular function of hypothyroid patients (Lauritano et al., 2007). Furthermore, Bifidobacterium and Lactobacillus (considered as probiotics) and Clostridium and Enterococcus were higher than in normal subjects, featuring an increased bacterial diversity in hyperthyroid patients (Zhou et al., 2014). Beside these two articles, thyroid/microbiota linkage was fairly disregarded as only two more review articles (Mori et al., 2012; Virili and Centanni, 2015) were published on this topic.

* Corresponding author. Department of Medico-Surgical Sciences and Biotechnologies, Corso Della Repubblica 79, 04100 Latina, Italy.
E-mail addresses: camillavirili@libero.it (C. Virili), marco.centanni@uniroma1.it (M. Centanni).

http://dx.doi.org/10.1016/j.mce.2017.01.053
0303-7207/

Nevertheless, thyroid hormone homeostasis is a complex and redundant system and the interference of microbiota on iodothyronine metabolism is an intriguing issue. Indeed, the overlooked part of the thyroid homeostatic mechanism is what happens in the gut where microbiota reigns supreme. This article aims to focus on the steps of iodothyronine metabolism which are possibly affected by the microbial composition of the gut. As such, our review has focused on the interaction of intestinal microbiota with thyroid-related micronutrients and the metabolic steps of endogenous and exogenous iodothyronines.

2. Iodine and selenium

Intrathyroidal and peripheral iodothyronine homeostasis largely depends on the function of the entities (enzymes, ionic pumps, transporters) whose activity is modulated by iodothyronines themselves but also on the availability of two micronutrients: iodine and selenium. The gastrointestinal tract is the headquarters of nutrient absorption, where iodine was formerly reputed to be absorbed by passive diffusion. Upon the characterization of Na/I symporter (NIS) as the mechanism concentrating iodine in the thyroid (Eskandari et al., 1997) its presence has been characterized in some other tissues (stomach, breast, salivary gland etc) (Dohàn and Carrasco, 2003) including the brush border of the small intestine in rats and mice (Nicola et al., 2009). More recently, a further ubiquitous transporter has been detected, named Na+/multivitamin transporter, which may represent a complementary structure for the intestinal absorption of iodine (de Carvalho and Quick, 2011).

How and whether microbial composition may affect iodine absorption in rats was studied some 50 years ago by treating them with kanamycin, a nonabsorbed oral antibiotic that reduces both aerobic and anaerobic bacteria concentration. In these treated rats, radioiodine uptake at 3 h was lower than in untreated rats, after 42 and 72 days of treatment (Vought et al., 1972). However, in parenterally nourished people with short gut syndrome, the urinary excretion of iodine was similar to that in control patients (Navarro et al., 2005), despite a serious imbalance of intestinal microbial composition (Piper et al., 2016). This finding has even been confirmed in patients who have undergone malabsorptive bariatric surgery, a further cause of microbial variation (Michalaki et al., 2014). So far, iodine absorption seems to be affected by microbial composition, whereas its urinary excretion is not. Overall, due to the weak evidence available, no conclusions can be drawn about the net peripheral iodine homeostasis.

Unlike iodine, the link between microbial composition and selenium availability appears to be closer. Selenium naturally occurs in both an inorganic (mineral or metallic) or organic form (selenomethionine and selenocysteine) (Khanam and Platel, 2016). Its biological action is exerted as an obliged constituent of the selenoproteins (Köhrle, 2015), the best characterized being glutathione peroxidase, which, beside other functions, prevents lipid peroxidation; thioredoxin reductase, which is chiefly involved in the machinery of nuclear redox; and deiodinase isoforms which regulate peripheral thyroid homeostasis (Köhrle, 1996; Khanam and Platel, 2016). Selenium absorption takes place in the duodenum and at the caecum and may vary depending on its chemical form (Mehdi et al., 2013). The thyroid possesses the highest selenium content per gram of tissue of the whole body (Duntas, 2015). It has been estimated that ¼ of total bacteria possesses selenoprotein-encoding genes. Some of these, such as Escherichia Coli, Clostridia and Enterobacteria, are able to colonize the gastrointestinal tract of humans and animals (Hrdina et al., 2009).

In a very recent study using an *in vitro* gastrointestinal digestion procedure model (Lavu et al., 2016), it was proven that selenium not absorbed in the small intestine may be actively taken up in the colon and metabolized by the resident microbes. This represents a real competition for the substrate (selenomethionine being the preferred substrate) which causes a reduction of selenium bioaccessibility, as shown by the reverse effect exerted by the presence of an inactive microbiota (Lavu et al., 2016). This finding is in keeping with a previous one (Hrdina et al., 2009) in which the expression analysis of gastrointestinal selenoprotein isoforms revealed that bacteria may compete with the host, chiefly in the presence of limited selenium supply. This increased selenium uptake by the intestinal bacteria may negatively influence selenoprotein expression in the host (Kasaikina et al., 2011). Furthermore, selenium enrichment in the diet increased the biodiversity of host microbiota, supporting the notion that this micronutrient may also shape intestinal microbial composition (Kasaikina et al., 2011) in a bidirectional fashion, related to the different utilization and toxicity profile of the bacteria.

3. How microbiota may influence the pathways of iodothyronines metabolism

Deiodination and conjugation pathways are the most effective in the whole metabolism of iodothyronines (Bianco and Kim, 2006). Almost 80% of thyroxine is deiodinated whereas the clearance of triiodothyronine is divided equally between deiodination and alternative pathways (Rutgers et al., 1989). These latter are, beside conjugation, oxidative deamination, alanine side chain decarboxylation as well as ether bond cleavage (Visser, 1996). However, some steps of iodothyronines metabolism may be affected by microbiota composition and are briefly discussed below.

3.1. Iodothyronines' binding and uptake

Since the early 60ˢ, *in vitro* studies have shown high affinity binding (T3 > T4) (Roche and Michel, 1960) and uptake (Salvatore et al., 1963) of radioactive iodothyronines in cultured *Escherichia coli*, a Gram-negative bacterium which is a major component of physiologic intestinal flora. In these cultured bacteria, deiodination, decarboxilation and deamination of iodothyronines have also been detected (Grasbeck et al., 1963; Roche and Michel, 1960; Salvatore et al., 1963).

In 1967**,** Chung and Van Middlesworth showed that bacteria in the intestine of normal rats are able to bind T4. This finding was later confirmed by Di Stefano III et al. (1993) who demonstrated a reversible *in vivo* binding of radiolabeled T3 and T4 in the feces and caecum contents of normal rats that was abolished or reduced in samples taken from antibiotic treated rats suggesting that the intestine may play a relevant role as a reservoir of an exchanging pool of iodothyronines; a pH-dependent oxidative degradation of T3 and T4 by intestinal flora was also observed.

3.2. Deiodinase activity

The explanation of these seminal observations became evident when the presence of deiodinase was detected in several of the rat's tissues, including the intestinal wall (Galton et al., 1991). These enzymatic activities have also been shown in the intestinal content of adult rats being inhibited by the resident microflora (Nguyen et al., 1993). In fact, they proved that both 5-D and 5′-D activities exist in adult rat intestinal contents possibly of cellular origin. In fact, the maximal deiodinase activity was found in frozed/defrosted samples, a step designed to rupture any cells in the media. Their activity was reduced or eliminated by the presence of normal intestinal bacteria. The authors postulated that the observed inhibition might be attributed to bacterial binding of T3 and T4. The

Please cite this article in press as: Virili, C., Centanni, M., "With a little help from my friends" - The role of microbiota in thyroid hormone metabolism and enterohepatic recycling, Molecular and Cellular Endocrinology (2017), http://dx.doi.org/10.1016/j.mce.2017.01.053