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Review

Carotenoids and their conversion products in the control of adipocyte function, adiposity and obesity

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ABSTRACT

A novel perspective of the function of carotenoids and carotenoid-derived products – including, but not restricted to, the retinoids – is emerging in recent years which connects these compounds to the control of adipocyte biology and body fat accumulation, with implications for the management of obesity, diabetes and cardiovascular disease. Cell and animal studies indicate that carotenoids and carotenoids derivatives can reduce adiposity and impact key aspects of adipose tissue biology including adipocyte differentiation, hypertrophy, capacity for fatty acid oxidation and thermogenesis (including *browning* of white adipose tissue) and secretory function. Epidemiological studies in humans associate higher dietary intakes and serum levels of carotenoids with decreased adiposity. Specifically designed human intervention studies, though still sparse, indicate a beneficial effect of carotenoid supplementation in the accrual of abdominal adiposity. The objective of this review is to summarize recent findings in this area, place them in physiological contexts, and provide likely regulatory schemes whenever possible. The focus will be on the effects of carotenoids as nutritional regulators of adipose tissue biology and both animal and human studies, which support a role of carotenoids and retinoids in the prevention of abdominal adiposity.

Introduction

Carotenoids are lipophilic C-40-based isoprenoid pigments usually red, orange or yellow in color which are produced by plants and certain photosynthetic microorganisms. Primary dietary sources are fruits and vegetables, though they can also be obtained from bread, eggs, milk, beverages, fats, and oils. Of ~600 carotenoids in nature, ~50 are present in the human diet, but only six are ubiquitous in human serum, namely β-carotene (BC),[1] α-carotene, β-cryptoxanthin, lycopene, lutein, and zeaxanthin [1].

The main known function of carotenoids in humans is to serve as precursors of vitamin A related retinoids such as retinol, retinal and retinoic acid that play important roles in the visual cycle and in gene regulation linked to many developmental and physiologic processes [2]. Intact carotenoid molecules and carotenoid cleavage products other than the retinoids may have additional biological activities whose relevance for human health is still uncertain, including acting as antioxidants and blue light filters for photoprotection [3,4]. BC is the main provitamin A carotenoid in the human diet. Key to retinoid production from BC in mammals is the activity of β-carotene-15,15′-oxygenase (BCO1), a cytosolic enzyme that cleaves BC centrally into two molecules of retinal (also named retinaldehyde, Rald), which can be oxidized irreversibly to retinoic acid or reduced reversibly to retinol [5] (Fig. 1). BCO1 is specific for

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[1] *Abbreviations used:* ADH, alcohol dehydrogenase; ALDH, aldehyde dehydrogenase; AMPK, AMP-dependent protein kinase; atRA, all trans retinoic acid; BAT, brown adipose tissue; BC, β-carotene; BCO1, β-carotene-15,15′-oxygenase; BCO2, β-carotene-9′,10′-oxygenase; BMI, body mass index; C/EBP, CCAAT-enhancer binding protein; CD36, cluster of differentiation 36; CRABP, cellular retinoic acid binding protein; CRBP, cellular retinol binding protein; FABP, fatty acid binding protein; 11β-HSD1, 11β-hydroxysteroid dehydrogenase type 1; ISX, intestine-specific homeobox; LRAT, lecithin:retinol acyltransferase; LDLr, low density lipoprotein receptor; LPL, lipoprotein lipase; NF-κB, nuclear factor κB; Nrf2, nuclear factor erythroid 2-related factor 2; PPAR, peroxisome proliferator activated receptor; Rald, retinaldehyde; RAR, retinoic acid receptor; RBP (or RBP4), retinol binding protein; RBPR2, RBP receptor 2; RDH, retinol dehydrogenase; REH, retinyl ester hydrolase; ROS, reactive oxygen species; RXR, retinoid X receptor; SAT, subcutaneous adipose tissue; SR-B1, scavenger receptor class B, member 1; STRA6, stimulated retinoic acid 6; UCP1, uncoupling protein 1; VAT, visceral adipose tissue; WAT, white adipose.

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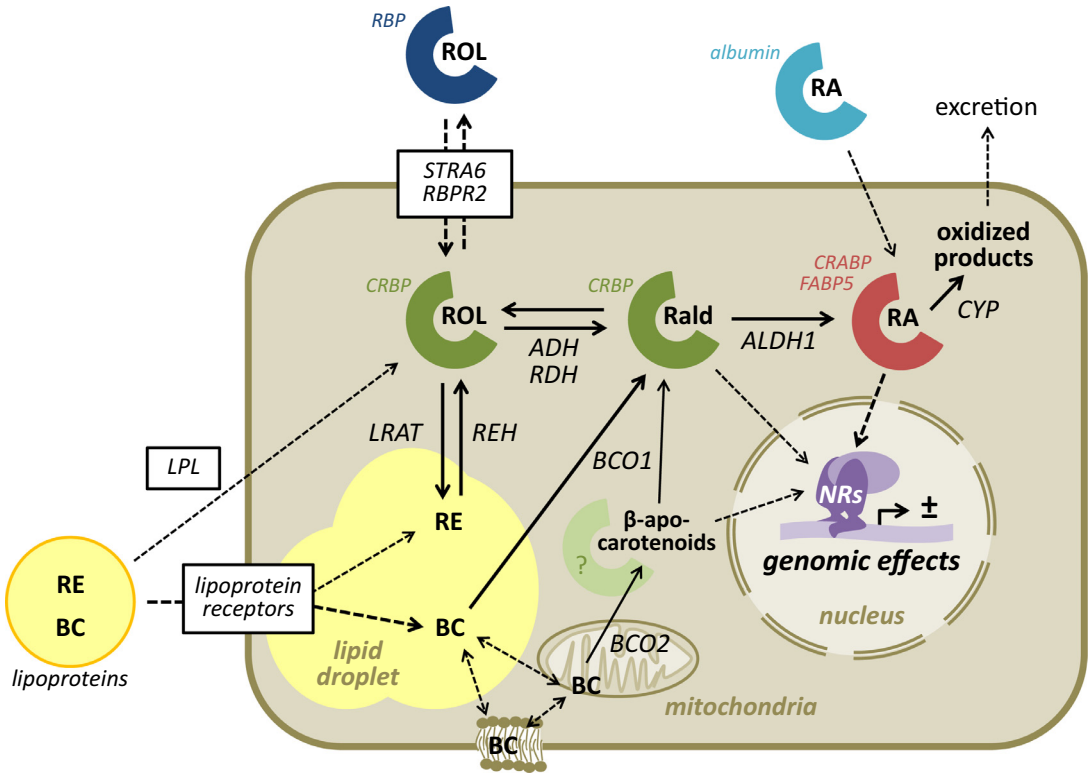

Fig. 1. Overview of cellular retinoid and β-carotene metabolism. Circulating retinol (ROL) bound to retinol binding protein (RBP) is internalized in peripheral cells through the action of specific surface receptors (STRA6, RBPR2) or by diffusion across the plasma membrane. Efficient ROL uptake depends on its binding to the cellular retinol binding protein (CRBP) and the activity of lecithin:retinol acyltransferase (LRAT) in esterifying ROL to fatty acids to form retinyl esters (RE) which incorporate into lipid droplets. RE associated with circulating lipoproteins can be hydrolyzed to ROL by lipoprotein lipase (LPL) and taken up by the cells. Alternatively, circulating lipoproteins containing RE and carotenoids such as β-carotene (BC) can be internalized in cells whole by endocytosis, mediated by lipoprotein receptors. Within the cell, RE is hydrolyzed by RE hydrolases (REH) to ROL, which can be reversibly oxidized to retinaldehyde (Rald) by short-chain dehydrogenase/reductases with retinol dehydrogenase (RDH) activity or medium-chain alcohol dehydrogenases (ADH) able to use retinol as a substrate. Rald can also be produced from BC, through symmetric cleavage catalyzed by β-carotene-15,15′-oxygenase (BCO1). BC (and other carotenoids, not shown) can be asymmetrically cleaved through the action of mitochondrial β-carotene-9′,10′-oxygenase (BCO2). Some BCO2 products can be converted into Rald, with the participation of BCO1. Rald is irreversibly oxidized to retinoic acid (RA) by the action of aldehyde dehydrogenases (ALDH1). RA can be taken up from the circulation where it is found bound to albumin. RA is transferred from the cytoplasm to the nucleus in association with specific intracellular lipid binding proteins (CRABP and FABP5). RA, Rald and other BC derivatives exert genomic effects by modulating the activity of distinct nuclear receptors (NR) and other transcription factors (not shown) in direct and indirect manners. These compounds exert as well non-genomic effects in cells (not shown). RA is catabolized by the cytochrome enzymes (CYP) to oxidative products that are eliminated from the cell.

provitamin A carotenoids containing at least one nonsubstituted β-ionone ring, such as BC, α-carotene and β-cryptoxanthin. Mammals express a second BC cleavage enzyme, β-carotene-9′, 10′-oxygenase (BCO2), which localizes to mitochondria, cleaves BC asymmetrically to generate diverse β-apocarotenals and β-apocarotenones, and has a broad substrate specificity as it metabolizes, for instance, the acyclic carotene lycopene and oxygenated carotenoids (i.e. xanthophylls, such as lutein and zeaxanthin) besides cyclic carotenes [5]. BCO1 and BCO2 are broadly expressed in mammalian tissues; such widespread expression, together with the wide distribution of carotenoids in animal tissues, has suggested that local, tissue-specific conversion of carotenoids may contribute to the *in situ* generation of retinoids and other apocarotenoids that impact tissue metabolism [5].

In recent years, a novel perspective of the function of carotenoids and carotenoid-derived products – including, but not restricted to, the retinoids – is emerging that connects these compounds to the control of body fat accumulation, with implications for the management of obesity and obesity-related metabolic disturbances [6–10]. Although effects on body fat content can relate to action in different tissues – among them the liver, which constitutes the main reservoir for carotenoids and vitamin A and whose lipid metabolism is indeed affected by retinoids [10] – cell and animal studies indicate that adipose tissue is an important target of carotenoid action. This evidence is the focus of this review. We begin by briefly presenting mechanisms of action that underlie the biological activity of carotenoids and carotenoid cleavage products, and the various lines of evidence that implicate these compounds as players in adipose tissue biology. While BC as the main provitamin A carotenoid is in the center of this review, other carotenoids active in the modulation of adipocyte biology and body adiposity are also given consideration. We review the impact of these compounds on body adiposity and their interaction with key aspects of adipose tissue biology as revealed by cell and animal studies, namely: adipocyte differentiation, adipocyte capacity for fat storage and oxidative metabolism/thermogenesis, and the secretory and inflammatory profile of adipose tissue. Human epidemiological and intervention studies addressing the relationship between carotenoids and vitamin A status and obesity and related metabolic diseases are specifically addressed.

Mechanisms of action of carotenoids and carotenoid derivatives

Collectively, carotenoids and carotenoid conversion products have been shown to impact gene expression and cell (including adipocyte) function through multiple mechanisms, notably by: (a) interacting with several transcription factors of the nuclear receptor superfamily, such as the canonical retinoic acid receptors

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