Retinoids and Carotenoids in Dermatology

Edited by

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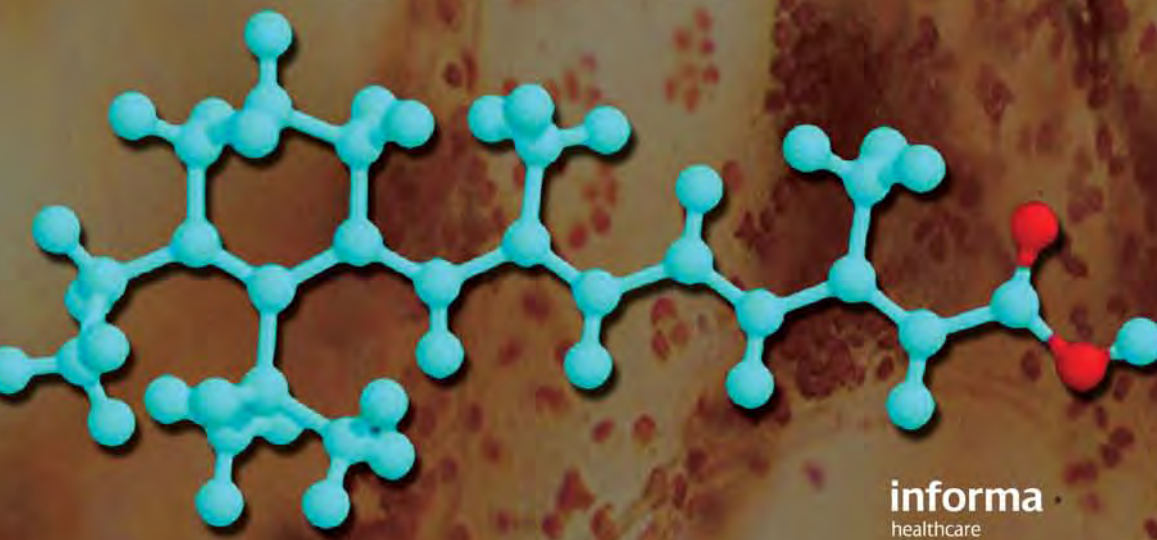

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Retinoids and Carotenoids in Dermatology

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healthcare

New York London

Informa Healthcare USA, Inc.
52 Vanderbilt Avenue
New York, NY 10017

Printed in the United States of America on acid-free paper
10 9 8 7 6 5 4 3 2 1

International Standard Book Number-10: 0-8493-3992-8 (hb: alk. paper)
International Standard Book Number-13: 978-0-8493-3992-9 (hb: alk. paper)

Library of Congress Cataloging-in-Publication Data

Retinoids and carotenoids in dermatology / [edited by] Anders Vahlquist.
Madeleine Duvic.
p. ; cm. -- (Basic and clinical dermatology ; 39)
Includes bibliographical references and index.
ISBN-13: 978-0-8493-3992-9 (hb : alk. paper)
ISBN-10: 0-8493-3992-8 (hb : alk. paper) 1. Retinoids--Physiological effect.
2. Retinoids--Therapeutic use. 3. Carotenoids--Physiological effect.
4. Carotenoids--Therapeutic use. 5. Skin--Diseases--Chemotherapy. I. Vahlquist, Anders. II. Duvic, Madeleine. III. Series.
[DNLM: 1. Skin Diseases--drug therapy. 2. Carotenoids--pharmacology.
3. Carotenoids--therapeutic use. 4. Retinoids--pharmacology.
5. Retinoids--therapeutic use.
W1 CL69L v.39 2007 / WR 650 R4387 2007]

QP801.R47R473 2007
612.7'9--dc22 2007010808

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To my wife Carin, for all the lost hours of companionship.
Anders Vahlquist

To Mike, Whitney, and Alice.
Madeleine Duvic

Introduction

During the past 25 years, there has been a vast explosion in new information relating to the art and science of dermatology as well as fundamental cutaneous biology. Furthermore, this information is no longer of interest only to the small but growing specialty of dermatology. Clinicians and scientists from a wide variety of disciplines have come to recognize both the importance of skin in fundamental biological processes and the broad implications of understanding the pathogenesis of skin disease. As a result, there is now a multidisciplinary and worldwide interest in the progress of dermatology.

With these factors in mind, we have undertaken this series of books specifically oriented to dermatology. The scope of the series is purposely broad, with books ranging from pure basic science to practical, applied clinical dermatology. Thus, while there is something for everyone, all volumes in the series will ultimately prove to be valuable additions to the dermatologist's library.

The latest addition to the series, volume 39, edited by Drs. Anders Vahlquist and Madeleine Duvic, is both timely and pertinent. The editors are internationally respected for their basic science and clinical expertise in the molecular biology and clinical applications of retinoids and carotenoids, and have assembled an outstanding group of contributors for this latest addition to our series. We trust that this volume will be of broad interest to scientists and clinicians alike.

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Preface

There are numerous reasons for publishing a book that jointly focuses on retinoids and carotenoids and on their relevance in skin biology and dermatology. Retinoids (i.e., retinol and its analogs) and carotenoids are both chemically and biologically related; the latter molecules are all basically polyprenoids (i.e., consist of repeated isoprene units) and are more or less omnipresent in nature (1,2). Some carotenoids (principally beta-carotene) can be converted to retinoids in mammals and fishes via enzymatic cleavage, making them important precursors of vitamin A in the diet. Furthermore, both groups of compounds are characterized by the high number of synthetic derivatives that have appeared since the advance of organic chemistry in the 1940s. Yet, from a biologic and therapeutic standpoint, retinoids and carotenoids are often regarded as separate entities, probably because they are used for different indications and have profoundly different dose-response curves.

Retinoid therapy, in the form of high-dose oral vitamin A, was initiated in the 1940s for hyperkeratotic skin diseases, but was later abandoned for toxicity reasons. Following the identification of all-trans retinoic acid as an active metabolite of vitamin A in the 1950s and the production of new retinoid derivatives in the 1970s with better therapeutic ratios in animal tumor models, some of these compounds (notably isotretinoin and acitretin) have since become a sine qua non for dermatology, especially in the field of acne, psoriasis, and keratinizing disorders. Subsequent to the discovery of retinoic acid receptors and their role in transcriptional regulation of important genes in the 1980s, a whole new paradigm has arisen where the strategy is to design specific ligands for the various retinoid receptors, aiming at fine-tuning the transcription machinery to mitigate various pathogenic mechanisms. As a direct consequence, new drugs and new indications for retinoid therapy have appeared, such as the use of oral bexarotene (targretin) in cutaneous lymphoma and alitretinoin (9-cis retinoic acid) in chronic hand eczema (3), and targretin gel has been used to treat chronic hand dermatitis and alopecia areata.

However, not all effects of retinoids are mediated by nuclear receptors, a fact that should not be overlooked when designing new drugs in this field.

Regrettably, throughout the process of developing new retinoids, toxicity problems (teratogenicity, etc.) have remained an insurmountable obstacle that necessitates strict precautions when prescribing oral formulations. Therefore, this book not only discusses the side effects and how to avoid them, but also focuses on useful knowledge about the pharmacology and various peculiarities of retinoid pharmacodynamics that underlie the untoward effects.

Carotenoids, on the other hand, are compounds that are much less toxic and are mainly known in human medicine for their antioxidant properties. They are prescribed by dermatologists to patients with various photosensitivity syndromes (e.g., protoporphyria), most often in the form of oral beta-carotene. Canthaxantin is another carotenoid that was popular in the 1980s as artificial skin pigmentation, but it was withdrawn from the market due to a hazardous accumulation in the retina after oral administration. More recently, a variety of other carotenoid molecules have been re-examined in the field of dermatology and may eventually emerge as approved drugs. Carotenoids are thought to play a significant part in the skin's natural antioxidant defense system and may also help prevent malignancy in other organs. This has led to an interest in monitoring the individual's carotenoid status, for example, by using such noninvasive techniques as Raman spectroscopy of the skin, showing a good correlation to the blood levels of carotenoids. Although the promising anti-tumor effects of carotenoids (and retinoids) originally observed in animal experiments have been somewhat disappointing when translated to the human situation, there are several indications that this may change in the future.

Although carotenoids in their capacity as lipid-soluble antioxidants and scavengers of free radicals seem to operate in human tissues mostly via non-genomic mechanisms, recent studies indicate that they may also affect more specific cellular functions. So, in this sense also, carotenoids and retinoids may again be merging and we may benefit from a combined approach when describing the mechanism of their action.

The primary objective of this book is to describe how retinoids and carotenoids function in the skin, and how they can be used as powerful agents to prevent and treat skin diseases. Although the emphasis of this book is on the clinical aspects of these compounds, several chapters are devoted to new basic research that is being done despite the adverse reactions that can especially characterize the retinoids. It goes without saying that this treatise is not strictly confined to dermatological aspects, but also describes important developments in other fields of retinoid and carotenoid research, especially in relation to cancer and immunology. Furthermore, the book provides a means for some readers to update their knowledge about biomedical issues outside the field of dermatology, such as general vitamin A nutrition, the role of antioxidants in aging, metabolic activation and degradation of polyprenoids, cellular signalling, inflammation, and the role of lipoproteins in atherosclerosis.

In organizing the book we included chapters written by internationally recognized authorities with widely different backgrounds, ranging from biochemistry and nutrition to molecular biology and clinical science. It is our hope that this broad approach attracts not only dermatologists, but also other clinicians and scientists with a general interest in retinoids, carotenoids, and the biology of the skin. We wish to express our sincere gratitude to all authors for their valuable contributions.

Anders Vahlquist
Madeleine Duvic

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From Carotenoids and Vitamin A to Retinoids

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INTRODUCTION

For more than 75 years, it has been known that vitamin A is critically important for growth and differentiation of epithelial cells, and it was soon realized that β-carotene is a provitamin that can replace vitamin A in the diet (1). As early as 1925, Wolbach and Howe (2) showed that vitamin A deficiency in rats led to the replacement of differentiated mature epithelium with squamous, keratinizing epithelial cells: Hyperkeratosis was observed in the skin, while hyperplastic and metaplastic changes were observed in epithelia of mucous membranes in vitamin A deficient rats. They concluded that vitamin A influenced the differentiation of epithelial cells, from the normal, simple, and pseudostratified phenotype to squamous, metaplastic lesions that start focally and spread throughout the epithelium. Shortly after, Nicholls (3) described phrynoderma, a distinct form of follicular hyperkeratosis, in African prisoners who also had night blindness and xerophthalmia (4). When treated with vitamin A containing cod live oil, both skin lesions and night blindness improved. In 1953, Fell and Mellanby (5) reported that the phenotype of chick epidermis in organ culture could be changed from keratinized to mucus-producing tissue by treatment with retinol or retinyl acetate. These

observations were followed by numerous studies focusing on the pharmacological action of retinoids and carotenoids in skin. This has ultimately resulted in the development of some thousand new synthetic compounds and the establishment of retinoids and carotenoids as treatment for various skin diseases (6–11). During the last years, the ability of retinoids to affect the gene expression and differentiation of epithelial cells in vivo and in vitro has been studied in great detail.

Today we know that vitamin A is essential for the life of all chordates, and has important functions, not only in maintenance of epithelial surfaces, but also in numerous other functions or processes such as vision, immune competence, reproduction, hematopoiesis, and embryonic growth and development. The major disciplines for vitamin A research include molecular-, cell- and developmental biology, dermatology, oncology, and public health, but potential roles are being explored in almost every field of biomedical research.

The aim of this introductory chapter is to describe relevant biochemical and cellular aspect of retinoid and carotenoid metabolism as a foundation for the succeeding chapters on specific topics related more directly to dermatology. A more comprehensive and neurobiology-related version of this chapter was recently published, and may serve as a source for further references and details (12).

NOMENCLATURE, STRUCTURE, AND CHEMICAL PROPERTIES

The term "vitamin A" is defined as the generic descriptor for all C_{20}-β-ionone derivatives that qualitatively exhibit the biological activity of all-*trans*-retinol. The term "provitamin A" is restricted for the carotenoids giving rise to vitamin A (Fig. 1) (13). Chemically, vitamin A belongs to the "retinoids," which are defined as a class of compounds consisting of four isoprenoid units joined in a head-to-tail manner. Thus, all retinoids may be formally derived from a monocyclic parent compound containing five carbon–carbon double bonds and a functional terminal group at the terminus of the acyclic portion. By this definition, retinoids would include both the naturally occurring forms of vitamin A as well as the many synthetic analogs of retinol, with or without biological activity. One problem with this definition is the fact that several synthetic compounds, which do not fit into the definition of retinoids have been shown to be much more active than retinol or retinoic acid in several assays for vitamin A or retinoid activity. It was therefore proposed (14) that "a retinoid should be defined as a substance that can elicit specific biologic responses by binding to and activating a specific receptor or set of receptors." In practice, most researchers today use a combination of these two definitions, that is, the class of retinoids consists of retinol analogs (with or without biologic activity) but also of several compounds, which are not closely related to retinol but elicit biological vitamin A or retinoid activity.

Several thousand synthetic retinoids have been developed. Synthetic agents that specifically bind to retinoid X receptors (RXR) are called rexinoids (15), whereas synthetic compounds that have lost the ring structure are called acyclic retinoids or acyclic rexinoids.

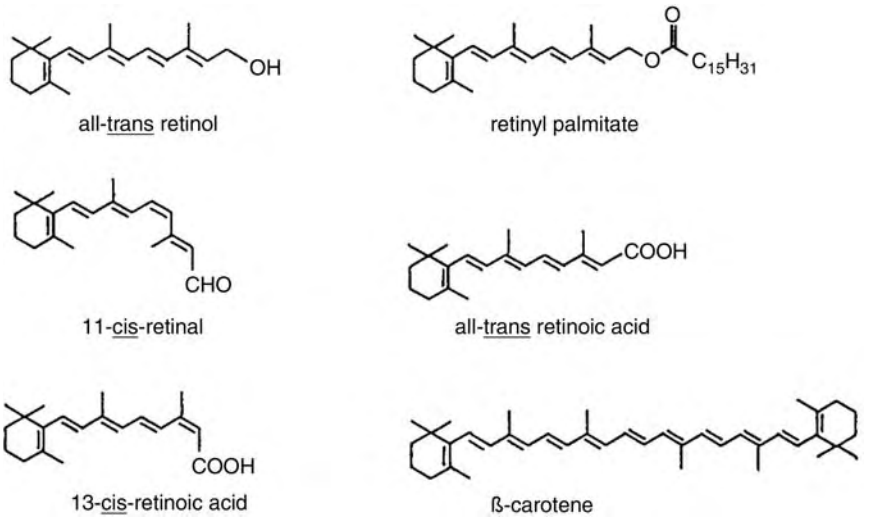

Figure 1 Structural formulas of some retinoids and β-carotene.

The parent retinoid compound all-*trans* retinol is a primary alcohol with molecular weight 286. In most animal tissues, the predominant retinoid is retinyl palmitate, but other fatty acid esters, such as retinyl oleate and retinyl stearate, are also found. Most of these metabolites occur in the all-*trans* configuration. The 11-*cis* aldehyde form, 11-*cis* retinal, is present in the retina of the eye, and several acid forms such as all-*trans* and 13-*cis* retinoic acid, are metabolites of retinol found in many tissues (Fig. 1). As discussed later, many more metabolites of retinol are detected in different cells and tissues. Still, too little is known about the role of these retinoids: they are presumably intermediates in the activation or degradation of retinol.

All-*trans* retinol and its derivatives are highly unstable in the presence of oxidants and light, which leads to their oxidative degradation or isomerization (16). These properties require tissues containing retinoids as well as retinoid standard solutions to be stored and handled experimentally in an inert atmosphere and under dim illumination (17,18).

Vitamin A (all-*trans* retinol) is a fat-soluble vitamin. Many binding proteins are therefore involved in transport of retinoids through hydrophilic phases such as plasma and extra- and intracellular fluids. Many retinoids, however, are also soluble to some extent in fluids such as plasma. The water solubility at room temperature and pH 7.3 of all-*trans* retinol, all-*trans* retinal and all-*trans*-retinoic acid is 60 nM, 110 nM, and 210 nM, respectively. This feature makes all-*trans* retinoic acid an ideal morphogen with ability to diffuse efficiently through water-soluble phases as well as hydrophobic membrane.

Originally, international units (IUs) (1 IU = 0.3 μg of all-*trans* retinol) were used for nutritional recommendations of vitamin A. Later, "retinol equivalents" (RE) were used to convert all sources of preformed retinol and provitamin A carotenoids in the diet into a single unit. When defining RE it was assumed that the absorption of provitamin A carotenoids was relatively efficient. Recent studies document, however, that absorption of carotenoids is much lower and appears to be quite variable. In addition, a number of factors such as protein-energy malnutrition, zinc-deficiency, dietary fat, alcohol, infections, and degree of food processing/food matrix affect the bioavailability and bioconversion of retinol and carotenoids. Based on these studies which are limited and not conclusive as yet, it is now generally assumed (19) that 1 retinol activity equivalent (RAE) is equal to 1 μg of dietary or supplemental preformed vitamin A (i.e., retinol), 2 μg of supplemental β-carotene, 12 μg of dietary β-carotene, or 24 μg of other dietary provitamin A carotenoids (e.g., α-carotene and β-cryptoxanthin).

DIETARY UPTAKE OF CAROTENOIDS AND VITAMIN A

No animal species are capable of de novo vitamin A synthesis. However, plants and some bacteria, algae and fungi can synthesize carotenoids, some of which can be converted to vitamin A in animals. The carotenoids represent a large group of pigments that are widespread in nature and responsible for the yellow, orange, red, or purple colors of many vegetables, fruits, and flowers (20). Many of these carotenoids can be absorbed and stored in animals, and often to such a degree that they give color to animal tissues. For example, lutein and zeaxanthin are concentrated in human macula, lycopene in human prostate, β-carotene in bovine corpus luteum and chicken egg yolk, astaxanthin and canthaxanthin in salmon flesh and flamingo feather (21). Animals and plants can cleave the carotenoids to form biologically active molecules, such as abscisic acid in plants, trisporic acid in fungi and retinoids in animals (22). Thus, carotenoids including α-carotene, β-carotene and β-cryptoxanthin are in animals like Drosophila, fish, chicken, mice, and humans, converted into retinal or apocarotenoids (which subsequently can be converted to retinoids), and animals can thereby obtain compounds with vitamin A activity from the diet.

As an alternative animals can obtain vitamin A from the diet by eating tissues from animals that already have converted the provitamin A carotenoids into retinoids. Thus, since retinyl esters, and to a lesser extent retinol, accumulate in fish-, avian-, and mammalian livers as well as in other animal tissues, these retinoids also contribute to the dietary intake of vitamin A. In Western countries, the intake of preformed retinyl esters or retinol typically account for 25% to 75% of the total vitamin A intake, with the rest being provided by provitamin A carotenoids (23). Retinoic acid from animal sources does not significantly contribute to the daily intake of vitamin A, since animal tissues typically contain only 3 to 15 μg retinoic acid per kg (24) (typical dietary retinol intake is about 1 mg/day for adults).