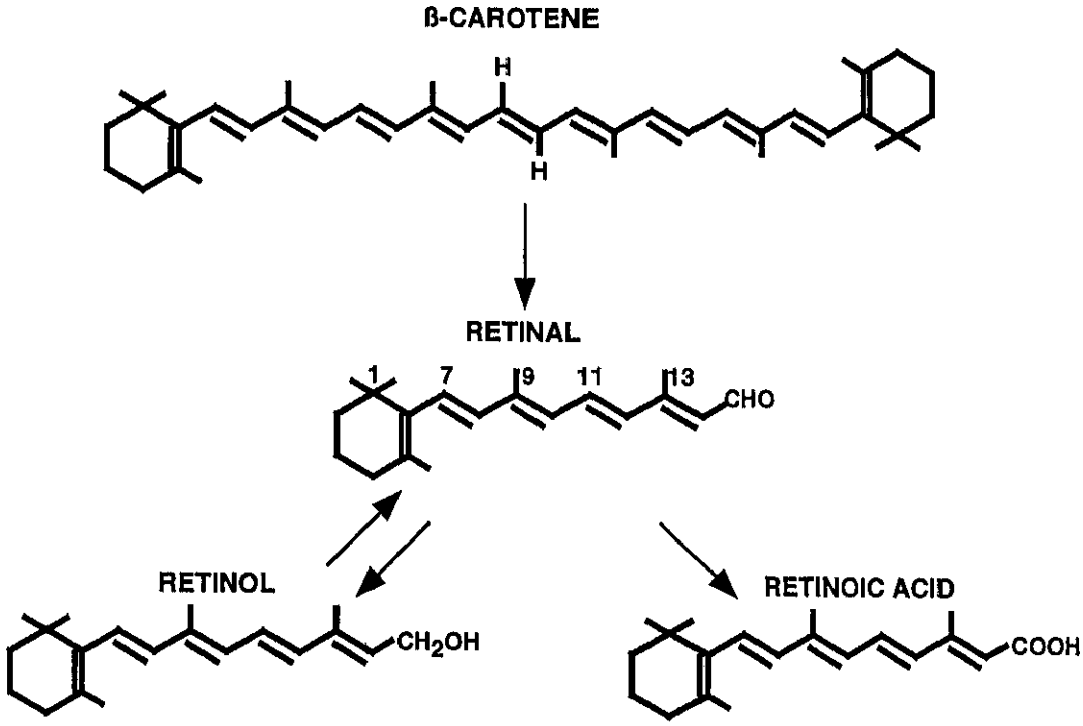
INTRODUCTION

Vitamin A is a fat-soluble physiological activator defined as the first fat-soluble nutrient essential for several life processes. Vitamin A is mainly derived from β-carotene that is composed of two vitamin A molecules (Fig. 1). After β-carotene is assimilated into the body, β-carotene is cleaved and oxidized to produce retinal, which, in turn, is reduced to retinol. Retinol is the primary form of the vitamin A. More than 95% of vitamin A in a whole body is stored at the liver as retinyl palmitate, an ester between retinol and palmitic acid. Liver monitors the blood concentration of vitamin A, and when the concentration becomes low, retinyl palmitate is readily hydrolyzed to release retinol into the blood circulation, maintaining blood vitamin A (retinol) concentration constant (about 1.7 μM) (1). It is well known that when liver received injury and undergoes process to the fibrosis/cirrhosis liver loses the stored vitamin A (2). However, the biological meaning of this phenomenon is unclear. Retinol is circulating as the complex with transthyretin and retinol-binding protein (1). At the target cells retinol is delivered inside of the cells through diffusion or by unknown mechanism(s), and is converted to retinal and further to retinoic acid (RA). The conversion between retinol and retinal is reversible, whereas the conversion of retinal to RA is irreversible. RA is thought to be the principal molecule for physiological action by vitamin A, because RA exerts the strongest activities among these three analogues of vitamin A, namely, retinol, retinal, and RA. Retinol, retinal, and RA are composed of a cyclohexenyl ring and a side chain containing four double bonds, resulting in the formation of many stereoisomers. Most predominant form of RA in the body is all-*trans*-RA (atRA). However, RA containing one *cis*-configuration, such as 9-*cis*-RA (9cRA), 11-*cis*-RA, or 13-*cis*-RA (13cRA) is also detected.



Biological roles of Vitamin A
1. Vision
2. Growth promotion
3. Differentiation and maintenance of epithelial tissue
4. Reproduction
5. Chemotherapy against a certain kind of cancer

Fig. 1. Chemical structure of vitamin A. β-carotene is composed of two vitamin A molecules. β-carotene is converted to retinal by a central oxidative cleavage, and then reduced to retinol. The liver stores most of vitamin A as the storage form of retinol such as retinyl palmitate and, when necessary, hydrolyzes the ester and releases retinol into the blood circulation. At the target cells retinol is converted to retinal and further to RA and exerts the biological activities.

It is well known that the deficiency in vitamin A causes night blindness because retinal serves as a photoreactive component of rhodopsin in the visual cycle (3). However, the biological roles of vitamin A are not limited to the visual cycle. Vitamin A exerts the diverse biological activities throughout the whole body by regulating cell growth, differentiation, and morphogenesis (3). For example, vitamin A mimics the action of morphogen in limb development, and the administration of vitamin A produces duplication in the finger pattern (4). Clinically, vitamin A is used as an important ointment for the treatment of skin diseases and has shown great promise as a novel anticancer or cancer-preventive agent (5); in the carcinogenesis of skin, lung, breast, and bladder, vitamin A effectively antagonizes the action of phorbol ester, that is a strong promoter of carcinogenesis. For a certain leukemia, vitamin A (RA) is used as a chemotherapy reagent (5). Along with the development of the molecular and cellular biology, the studies of vitamin A have many opportunities for discussion from biological and medical viewpoints. Today, vitamin A and its natural or synthetic derivatives are called "retinoids" in the field of biology and medical sciences, and many investigators study the molecular mechanisms of retinoid action.

The understanding of the molecular mechanism of retinoid has been greatly advanced by a discovery of the nuclear retinoid receptors (6,7). This finding has established the concept that retinoid signals can be transduced at transcriptional level, namely that retinoids regulate the gene expressions and, therefore, exert a variety of biological activities. Nuclear retinoid receptors belong to the largest family of transcription factors, so far known today, many of which act as ligand-dependent transcriptional activators and modulate the expression of target genes by binding to cognate DNA elements. However, many questions remain to be elucidated. For example, not all RA-inducible genes contain a cognate DNA binding sequence for the receptors. It can be said

that the molecular mechanisms of retinoid action are on a mid-way to be analyzed at the molecular levels.