

RETINOIDS

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Medical Pharmacology

OVERVIEW

Retinoids comprise a family of polyisoprenoid lipids which include vitamin A (retinol) and its natural and synthetic analogs. Vitamin A deficiency is ranked along with protein calorie malnutrition and iron deficiency anaemia as one of the three top priority nutritional diseases. Vitamin A blindness is both the easiest and the cheapest major nutritional illness to cure .

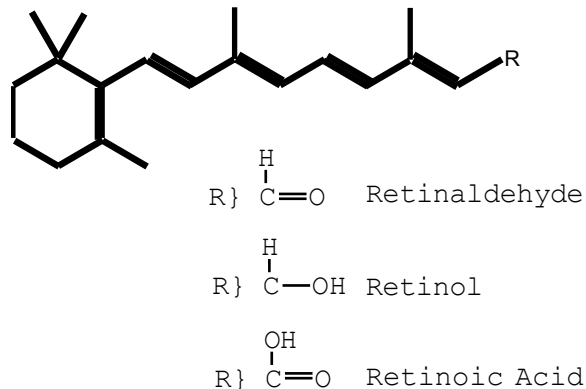
Retinoids are compounds with multiple actions. They are involved in the control of cell proliferation, cell differentiation, and embryonic development. Vitamin A is indispensable for embryonic pattern formation, for visual function, and the differentiation of epithelial tissues.

Vitamin A deficiency leads to many diseases including the hyperkeratosis of the skin and to hyperplastic and metaplastic changes in the epithelia of mucous membranes. This link is of interest to dermatologists and oncologists.

Great progress has been achieved with retinoids in treating dermatological diseases such as acne, psoriasis, and other keratinizing disorders.

Retinoids are affective therapy for some precancerous lesions, the treatment of acute promyelocytic leukemia (APL), and the prevention of malignancies in high-risk cancer groups.

Each retinoid has its own profile of pharmacological properties that determine its usefulness in clinical dermatology or oncology. Although numerous synthetic retinoids have been synthesized, their biological activities are usually associated with clinical disadvantages such as toxicity and teratogenicity.



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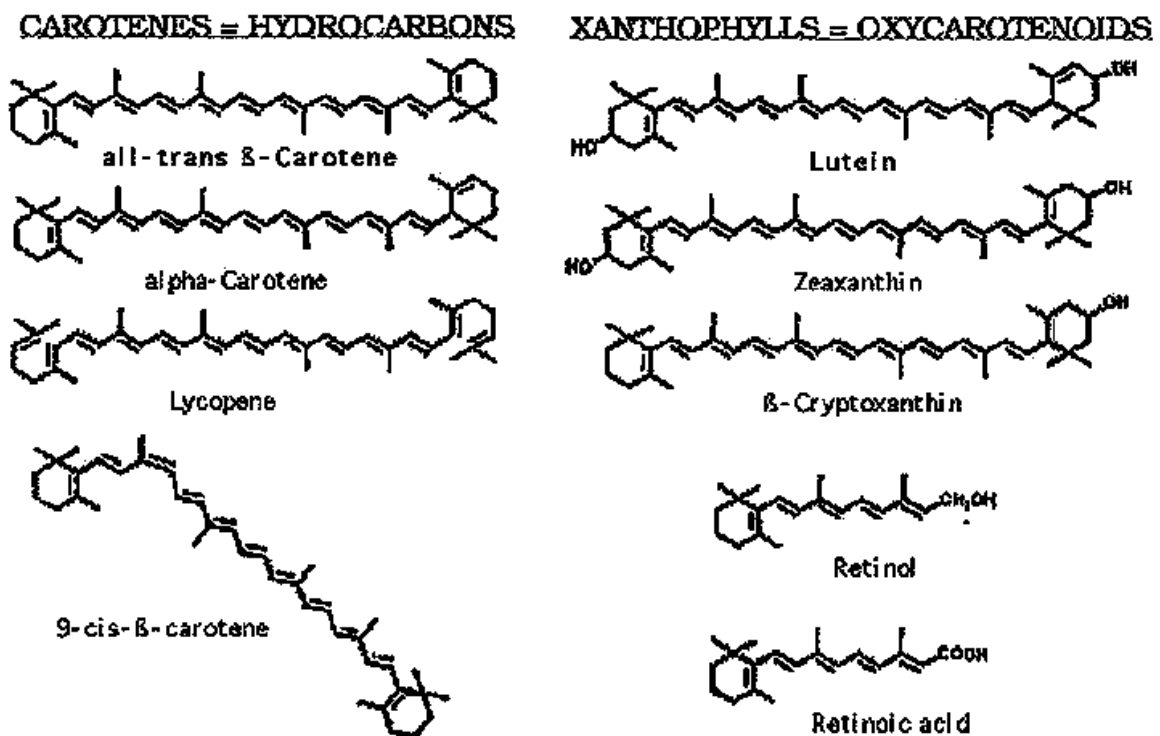
Chemistry, Metabolism

Retinol, retinaldehyde and retinoic acid are collectively known as Vitamin A. Vitamin A is necessary for maintenance of healthy epithelial tissue and can prevent the inception or progress of skin cancers by stimulating normal cell differentiation.

Retinol is not obtained directly from the diet, but rather is generated in the intestine from the enzymatic cleavage of beta-carotene, alpha-carotene and beta-cryptoxanthin. Beta-carotene yields 2 molecules of retinal. The carotenoids are ultimately produced by plants and other photosynthetic organisms.

Animal products such as egg yolk, milk, liver and fat contain retinyl esters which are hydrolyzed to retinol in the intestine.

Retinal (from beta-carotene) is converted to retinol for membrane transport, and converted back to retinyl esters for cellular storage.



In the target cells, retinol is oxidized to retinal and retinoic acids. The latter regulate growth/differentiation of epithelia/mesenchymal cells.

Retinal is utilized in the synthesis of rhodopsin in the cones, and is necessary for night vision.

Protein binding, Absorption and Transport

Retinol is transported in serum to target cells complexed with specific retinol-binding proteins (see below), esterified to R-FA (retinyl esters) by the enzyme lecithin:retinol acyltransferase (LRAT), and incorporated into lipoprotein particles (called chylomicrons in humans).

How retinoids are stored, transported and metabolized:

- * A specific circulatory transport system for retinol is mediated by serum retinol-binding protein (RBP).
- * Retinoids readily accumulate in the liver, the major storage organ. Liver also synthesizes most of the circulatory RBP.
- * The nuclear receptors RAR and RXR (see below) can shuttle retinoids, from cytoplasm to nucleus.
- * There are also cytosolic retinoid-carrier proteins (CRBPI and CRBPPII).
- * These three groups of retinoid-binding proteins control most of the non-visual physiological effects of the vitamin A family of molecules.

Target Cells and Tissues:

- * Intestinal lumen: dietary retinyl esters are converted to retinol by pancreatic enzymes.
- * Small Intestinal Absorptive Cell: retinol diffuses across the luminal membrane and binds CRBPPII for transport to the serosal surface. It is re-esterified with palmitate and incorporated into chylomicrons from which retinol is released into the blood.
- * Blood vessels: retinol in the blood binds RBP. When RBP is deficient, or Vitamin A is in excess, retinyl esters bind plasma lipoproteins forming surfactants which can damage cell membranes. Retinoic acid does not bind RBP but does bind albumin.
- * Hepatocyte: retinol is delivered via endocytosis of chylomicrons from which it is re-esterified for cellular storage and de-esterified for release of retinol back into blood when free RBP exists.
- * Target epithelial/mesenchymal cells: Retinol enters the cell and binds to CRBPI. It is re-esterified for storage and esters are hydrolyzed to release retinol. Retinol is oxidized to retinoic acid (RA) for binding to specific nuclear receptors (RAR and RXRs).

Retinoids in the visual Cycle

The chromophore of the visual receptors, in the rods and cones of vertebrate and invertebrate retina, is (universally) *11-cis* retinal. The primary light transduction event is its isomerization to *all-trans* retinal.

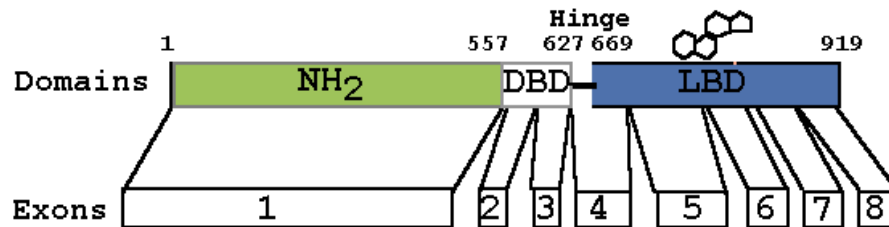
Retinal deficiency leads initially to reversible, and ultimately to irreversible night blindness. Vitamin A deficiency is probably the foremost cause of preventable blindness in the world

The Nuclear Receptors for Retinoids (RAR, RXR)

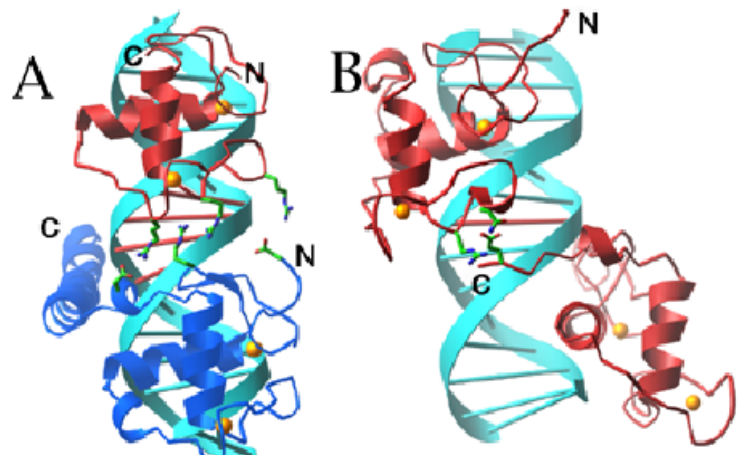
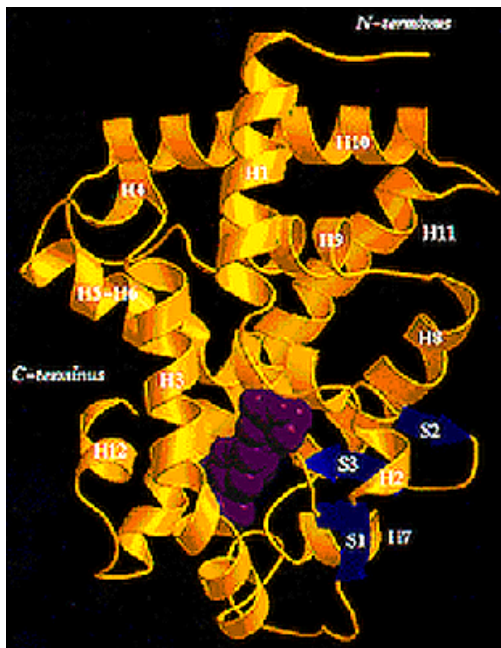
The signaling Pathway of retinoids involves specific nuclear receptors that regulate gene expression. There are specific nuclear receptors for retinoids. These receptors bind their retinoid ligands, target to

DNA response sites upstream of retinoid responsive genes, and up/down regulate transcription.

- * RAR is the receptor for *all-trans* retinoic acid.
RXR is the receptor for *9-cis* retinoic acid.
- * RXR and RAR belong to a large superfamily of related nuclear hormone receptors, which share a common architecture. There is a conserved DNA-binding domain (DBD), and a ligand-binding domain (LBD). These factors use their LBD to bind to their cognate



retinoids and their DBDs to bind to DNA response sites from which they regulate genes.



The ligand binding domain (LBD) of RAR bound to all-trans RA (CPK).

(A) RXR-RXR DN (DBD) Bound to DN

A-binding domain A. (B) RXR-TR. □

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- * RAR and RXR are related to each other in sequence and to the thyroid hormone receptor (TR), the vitamin D receptor (VDR), testosterone receptor, and 150 other hormone/steroid/orphan receptors all of which form the nuclear receptor family.

- * There are important cross interactions between RXR and other nuclear receptors: RXR forms heterodimers with RXR; for example RXR-RAR, RXR-VDR or RXR-TR. These receptor

heterodimers are the functional species that transmit the hormonal signals via genetic mechanisms. The role of RXR as a promiscuous dimerization partner may be related to the multiple effects of retinoids in mammals.

- * The receptor heterodimers interact with mediators (co-activators and co-repressors) and the basal transcriptional machinery (RNA Pol II) to regulate genes.

Cellular Responses

Reproduction and Embryonic Development: Gradients of retinoic acid act as morphogens to control embryonic development, well established for limb development. Consequently higher doses of many retinoids are teratogenic.

Epithelial and Fibroblast Growth and Differentiation: Retinoids:

- * Stimulate growth and differentiation of epithelial cells- skin, respiratory, mammary, urinary tract, GI.
- * Stimulate differentiation of basal epidermal Goblet cells which produce mucus (without RA, basal cells proliferate instead and generate keratinizing epithelium).
- * Increase production of fibronectin, epidermal growth factor receptors (EGFRs).
- * Decrease production of collagenase, keratin, sebum secretion, and 1,25-Vitamin D receptors (VDRs).
- * Bone Growth and Differentiation: RXR-VDR increase osteocalcin transcription.

Immune System Function:

promote differentiation of myelomonocytic precursors

increase IL2 receptor expression

inhibit release of arachidonic acid from macrophages.

Anti-Cancer Activities:

* Epithelial Cells:

RA promotes differentiation. Seems to work late in carcinogenic process, affecting the promotion and progression stages. Less effective at reversing growth of established metastases. Suppression of carcinogenesis in skin and bladder have been demonstrated experimentally. B-carotene may work as anti-oxidant by producing Retinoic acids.

* Mesenchymal Cells:

Induce differentiation of certain promyelomonocytic leukemias leading to clinical remissions.

inhibit angiogenesis, thereby having potential inhibitory effects on growth of solid tumors beyond certain size.

- * Endocrine Tissues: Some experimental evidence for growth inhibition of early prostate and breast cancers by retinoid analogs.

The Role of Altered Retinoic Acid Receptors in Cancer

Given the key role of retinoids in development, it was not surprising that acquired abnormalities in proteins implicated in the retinoid response pathways should be associated with disorders of either differentiation or proliferation.

Structurally and functionally altered retinoic acid receptors have been associated with rare human neoplasms: acute promyelocytic leukemia (APL) and hepatocellular carcinoma.

Hepatocellular carcinoma:

In a case of human hepatocellular carcinoma, the hepatitis B virus was found to be integrated in the gene for RAR-beta. A chimeric gene results.

Acute promyelocytic leukemia:

RAR-alpha gene fusion to the promyelocytic leukemia (PML) gene by a translocation event. The resulting PML-RAR fusion product appears to have transforming potential. (see Figure ahead).

Vitamin A deficiency

* Incidence: 3% of healthy US population; much of 3rd world- usually children.
Since levels are buffered by binding proteins and storage forms, it takes a long time to see symptoms.

* Symptoms:

- night blindness
- diarrhea due to lesions of intestinal epithelia
- thick cancellous bone in place of thinner compact bone
- reproductive abnormalities, slow growth
- decreased RBCs, blood volume
- effects on taste, smell, hearing.

Use of Vitamin A for deficient states- infants, pregnant or lactating women require 25% more. Also for cancer prophylaxis:

Hypervitaminosis A

Cause: excessive vitamin consumption, polar bear liver, retinoid drug therapy.

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Symptoms:

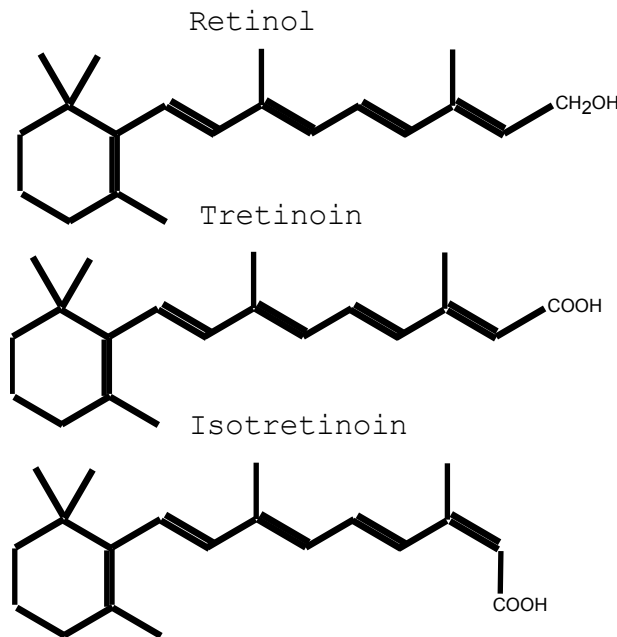
- dry, red, itching skin, desquamation, fissures of lips, hair loss, acute peeling.
- liver: hepatosplenomegaly, hypertrophy of fat storing cells, cirrhosis.
- congenital abnormalities with in utero exposure.
- miscellaneous: headache, anorexia, fatigue, hemorrhage, irritability.

Duration: weeks to months after stopping excess intake. Delay due to various storage forms of the vitamin. Vitamin E eliminates some Vitamin A toxicity.

Drugs: First generation Retinoic Acid Analogs

Description: these contain β -ionine ring.

There are two types of retinoic acids used in therapy: tretinoin (trans-retinoic acid) and isotretinoin (13-cis-retinoic acid or Accutane). Both of these drugs are derivatives of Vitamin A and are used to treat skin disorders such as acne. The treatment for cystic acne is effective, but also causes some side effects (see below).



Isotretinoin

(13-cis retinoic acid). Trade names: Accutane, Roaccutane, Accure, IsotrexGel.

* Availability: in tablet or gel.

Usage: Isotretinoin is indicated for the treatment of severe recalcitrant nodular acne. Nodules are inflammatory lesions with a diameter of 5 mm or greater. Isotretinoin, when administered in pharmacologic dosages of 0.5 to 2.0 mg/kg/day, inhibits sebaceous gland function and keratinization. The exact mechanism of action of Accutane is unknown.

Nodular Acne: Clinical improvement in nodular acne patients occurs in association with a reduction in sebum secretion. The decrease in sebum secretion is temporary and is related to the dose and duration of treatment with Accutane, and reflects a reduction in sebaceous gland size and an inhibition of sebaceous gland differentiation.

* Effectiveness:

1. Isotretinoin is used to treat severe acne that is resistant or minimally responsive to more conservative treatments such as creams, drying agents, and topical or oral antibiotics.
 2. Complete remission or prolonged improvement is often seen after one course of treatment.
 3. Because of its serious side effects, isotretinoin should be used only for severe resistant acne.
- * Pharmacokinetics: < 50% absorbed from gut. 25% of absorbed drug is converted to tretinoin (active form). Remainder is oxidized and/or conjugated and excreted in bile. Plasma half-life is =>24 hours, but some metabolites persist for 1-2 months. Not effective topically.
 - * Precautions: Isotretinoin must not be used by women who are pregnant, plan on being pregnant, or have a chance of becoming pregnant. Accutane causes severe birth defects. Abstinence or effective birth control methods should be used and pregnancy tests should be performed prior to starting treatment and monthly during treatment. Pregnancy should be avoided until at least one month after stopping isotretinoin. Nursing mothers should not use isotretinoin. Any woman of child bearing age should seriously discuss potential side effects with her doctor.
 - * Adverse Symptoms: Isotretinoin can cause worsening of night vision and decreased tolerance to contact lenses. Patients with inflammatory bowel disease can experience a worsening of symptoms. In order to avoid toxicity, patients taking isotretinoin should not use Vitamin A supplements. Patients treated with isotretinoin generally experience a worsening of the acne during the beginning of treatment.
 - * Toxic dosage:
 - Overdose has produced headache, facial flushing, vomiting, abdominal pain, dizziness and staggering.
 - Serious overdose is expected to cause symptoms similar to vitamin-A toxicity.
 - Changes in vision may indicate the beginning of toxicity to the cornea.
 - Increased intracranial pressure has been reported.
 - Symptoms include headache, vision changes, nausea

Tretinoin

(All-trans-retinoic acid), Brand Name is Retin A

Topical Tretinoin is used in the treatment of mild to moderate acne and on skin that has been damaged by excessive sun exposure. Tretinoin irritates the skin and causes the cells of the skin to grow (divide) and die more rapidly, that is, it increases the turnover of cells. The number of layers of cells in the skin actually is reduced. In patients with acne, new cells replace the cells of existing pimples, and the rapid turnover of cells prevents new pimples from forming. By a similar mechanism, Tretinoin can reduce some wrinkles, areas of darkened skin, and rough areas of skin, all of which occur in sun-damaged skin. In patients with sun-damaged skin, improvements in the skin usually are seen within the first 3 to 4 weeks of treatment. Brown spots begin to fade after six to eight weeks.

Wrinkles decrease or disappear after three to six months.

- * **Pharmacology:** The exact mode of action is unknown, current evidence suggests that topical tretinoin decreases cohesiveness of follicular epithelial cells. Additionally, tretinoin stimulates mitotic activity and increased turnover of follicular epithelial cells.
- * **Pharmacokinetics:** bound to albumin in plasma; rapidly metabolized in liver to inactive, or conjugated products. Very little systemic absorption from topical (gel) use.
- * **Adverse Reactions:**
The skin of certain sensitive individuals may become excessively red or crusted. Then, the medication should be adjusted to a level the patient can tolerate. Temporary hyper- or hypopigmentation has been reported with repeated application of Tretinoin.. To date, all adverse effects of Tretinoin have been reversible upon discontinuance of therapy.
- * **Overdosage:** If medication is applied excessively, no more rapid or better results will be obtained and marked redness, peeling, or discomfort may occur. Oral ingestion of the drug may lead to the same side effects as those associated with excessive oral intake of Vitamin A.

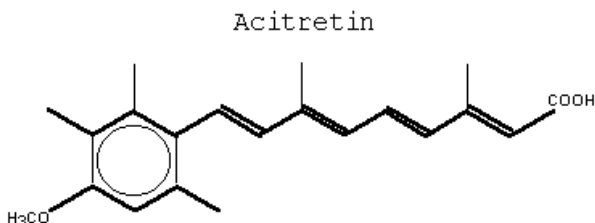
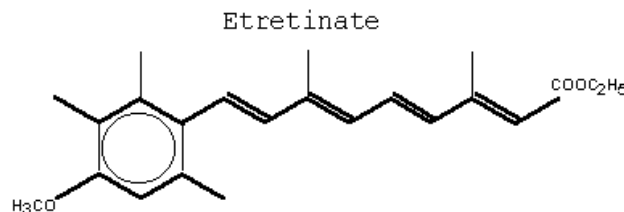
Therapeutic results: should be noticed after two to three weeks but more than six weeks of therapy may be required before definite beneficial effects are seen.

Once the acne lesions have responded satisfactorily, it may be possible to maintain the improvement with less frequent applications, or other dosage forms.

2nd Generation Drugs: Etretinate and Acitretin

Etretinate (Trade Names; Tegison and Soriatane) is the ethyl ester of Acitretin, both are shown below. The “2nd generation drugs” have aromatic ring in place of β -ionine ring (see picture below).

Usage: For psoriasis (scaly, rough and red patches), psoriatic arthritis (A rheumatoid-like arthritis associated with psoriasis of the skin or nails and a negative test for rheumatoid factor), ichthosis (excessive accumulation of scale).



Pharmacokinetics. 50% bioavailability, increases with food, milk, fat. converted to acitretin (active drug, see figure above) in gut and liver. Accumulate in plasma, fat, other tissues, with half-life of > 5 months.

Toxicity: common; symptoms of hypervitaminosis A. Requires contraception.

THIRD GENERATION DRUGS (Arotenoids):

These are just experimental at this stage. They have two aromatic rings, apparently more potent, with different spectrum of actions. Many under development for cancer prophylaxis. Attempts are being made to target specific RAR and RXRs to obtain improved specificity and decreased toxicity.

References:

Goodman & Gilman (9th Ed), Ch. 63.
The FASEB Journal Vol 10(9): July 1996.

Summary of Compounds and Drugs

Vitamin A	Isotretinoin				
Carotenoids	Etretinate	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Retinol	Arotenoids				
Tretinoin	Acitretin				