

Cellular metabolism and actions of 13-*cis*-retinoic acid

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Retinoids (vitamin A and its derivatives) are potent substances for regulating the expression of many different genes within the body. The gene regulatory activities of retinoids are mediated primarily by the all-*trans* and 9-*cis* isomers of retinoic acid. Although 13-*cis*-retinoic acid (isotretinoin) does not have the potent gene regulatory activity of the other two isomers, it is an effective pharmacologic agent for treating a variety of dermatologic conditions. Because 13-*cis*-retinoic acid is also a naturally occurring retinoid that is present in the circulation, question is raised as to the biochemical mechanism(s) responsible for its pharmacologic efficacy. Some of this efficacy likely arises from the ability of 13-*cis*-retinoic acid to undergo isomerization to the significantly more active all-*trans* and 9-*cis* isomers; however, this does not account for all of the pharmacologic effects observed upon use of this retinoid. Some recent studies suggest that 13-*cis*-retinoic acid may act by inhibiting the actions of enzymes that are needed to metabolize steroids, while other recent studies indicate that 13-*cis*-retinoic acid acts through membrane receptors present on the surface of cells. At the present, it is not possible to rule out still other possible biochemical actions of 13-*cis*-retinoic acid in the body. It is clear, however, that if we are to fully understand the basis for the clinical efficacy of 13-*cis*-retinoic acid, a better understanding of such biochemical actions is needed. (*J Am Acad Dermatol* 2001;45:S129-35.)

It is well accepted that 13-*cis*-retinoic acid (isotretinoin) is a naturally occurring form of retinoic acid that is normally present in blood and tissues of humans and higher animals.¹ Because 13-*cis*-retinoic acid is not as active in transactivation assays as the all-*trans*- and 9-*cis*-retinoic acid isomers,² it is also generally believed that 13-*cis*-retinoic acid is not a key retinoic acid form for regulating gene transcription. However, this retinoic acid isomer is effective, when given in large pharmacologic doses, in inducing retinoid-responsiveness in cells in culture and in animal models and in treating human disease, especially dermatologic conditions. It is thought that many of these actions by 13-*cis*-retinoic

acid are mediated by all-*trans*-retinoic acid, or possibly 9-*cis*-retinoic acid, after isomerization of the 13-*cis* isomer. Nevertheless, all of the actions of 13-*cis*-retinoic acid cannot be accounted for by the hypothesis that it acts solely as a precursor for the more transcriptionally active all-*trans*- or 9-*cis*-retinoic acid isomers. The simple substitution of either all-*trans* or 9-*cis* isomers for 13-*cis*-retinoic acid often does not fully replicate the same biologic response that is observed for 13-*cis*-retinoic acid.

This review will focus primarily on the current understanding of physiologic aspects of 13-*cis*-retinoic acid formation and actions. Some consideration will be given to 13-*cis*-retinoic acid metabolism on its pharmacologic administration to humans.

13-CIS-RETINOIC ACID: PHYSIOLOGIC CONSIDERATIONS

It has been known since the mid-1980s that 13-*cis*-retinoic acid is a naturally occurring retinoid form in animals.^{3,4} At this time, it was also shown that cultured rabbit tracheal epithelial cells can convert all-*trans*-retinoic acid to 13-*cis*-retinoic acid.⁵ Taken together, this work established that 13-*cis*-retinoic acid is a physiologically relevant endogenous retinoid found in higher organisms. Subsequent investigations extended this observation to humans by demonstrating that 13-*cis*-retinoic acid is present as an endogenous component of human serum.^{6,7}

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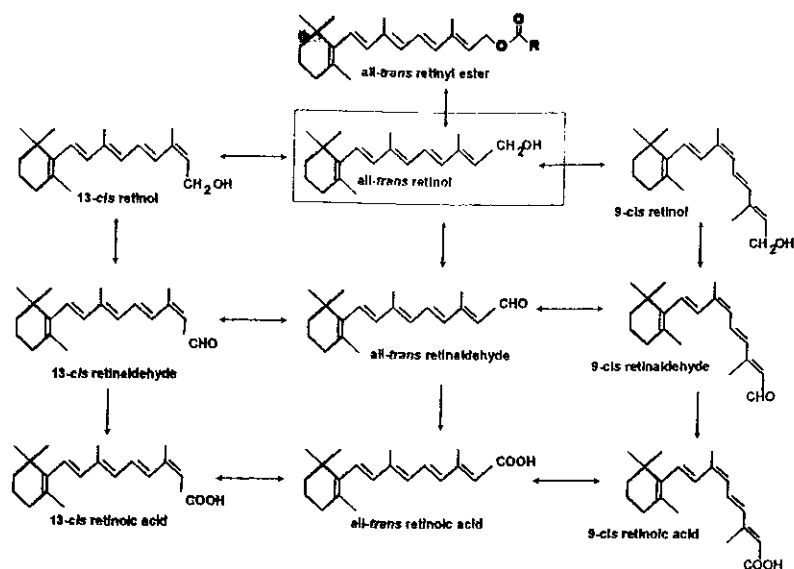


Fig 1. Hypothetical scheme for the biosynthesis of retinoic acid from retinol. The metabolic steps listed are the most extensively studied transformations and involve the oxidative metabolism of retinol to retinoic acid. Less well understood are the proposed *cis-trans* isomerizations.

Fasting serum levels of *all-trans*- and *13-cis*-retinoic acid range from 3.7 to 6.3 nmol/L and from 3.7 to 7.2 nmol/L, respectively. These levels rise after the consumption of vitamin A. It is now well established in the literature that, in humans, *13-cis*-retinoic acid is formed on the consumption of a dose of vitamin A. After the administration of a single oral dose of retinyl palmitate (vitamin A ester; 0.87 $\mu\text{mol/kg}$ body weight or 0.46 mg/kg body weight) to 20 volunteers, the concentration of *all-trans*-, *13-cis*-, and *13-cis*-4-oxo-retinoic acid in the plasma rose 2- to 4-fold with maximal concentrations observed at 1.5 to 6 hours after dosing. When the volunteers were dosed daily for a 20-day period with 0.87 $\mu\text{mol/kg}$ body weight of retinyl palmitate, plasma levels of *all-trans*- and *13-cis*-retinoic acid transiently increased but after 20 days returned to the initial levels.⁸ This effect of orally administered vitamin A on *all-trans*- and *13-cis*-retinoic acid levels has been confirmed by other studies that showed that (on the administration of either physiologic or pharmacologic doses of retinyl palmitate) plasma levels of *all-trans*- and *13-cis*-retinoic acid rose 1.3-fold and 1.9-fold, respectively, over fasting plasma levels.⁹ This observation regarding circulating retinoic acid levels also holds on the consumption of a vitamin A-rich meal. When volunteers were given a normal-sized meal of fried liver, plasma levels of *13-cis*-retinoic acid rose markedly in response to the meal.¹⁰ For these volunteers, 4 hours after consumption of the meal, mean plasma *13-cis*-retinoic acid concentrations were reported to rise approximately 19-fold

from 3.7 nmol/L to 72 nmol/L. Interestingly, for these studies, plasma levels of *all-trans*-retinoic acid did not respond as substantially as those of *13-cis*-retinoic acid and rose maximally only 2.5-fold from 2.7 nmol/L to 6.7 nmol/L. Thus, *13-cis*-retinoic acid is readily formed on the consumption of preformed vitamin A by healthy humans, and this holds true for both relatively large pharmacologic doses of vitamin A and for more physiologic doses and routes of administration of the vitamin A.

Although it is well established that *13-cis*-retinoic acid is present endogenously in the human circulation and that *13-cis*-retinoic acid levels in the circulation can be influenced by vitamin A intake, there are almost no data available regarding endogenous concentrations of *13-cis*-retinoic acid in other human tissues. This lack of information is, in part, due to the relatively short biologic half-life of *13-cis*-retinoic acid in living tissues and, in part, due to technical difficulties encountered in the accurate measuring of the relatively low concentrations of this labile retinoid that may be present in tissue biopsy specimens. Nevertheless, it is well established that *13-cis*-retinoic acid is present physiologically in a number of rat and mouse tissues,¹¹ and it is generally assumed that *13-cis*-retinoic acid is also widely distributed in human tissues.

FORMATION OF 13-CIS-RETINOIC ACID WITHIN THE BODY

Most of the retinoic acid present in the body is formed through sequential enzymatic oxidation of

retinol to retinal, followed by oxidation of retinal to retinoic acid.¹¹ This 2-step oxidation resembles ethanol oxidation and is depicted in the metabolic scheme provided in Fig 1. The most thoroughly investigated step of the metabolic steps shown in Fig 1 is the oxidation of all-*trans*-retinol to all-*trans*-retinoic acid. As is summarized in Table I, members of 2 enzyme families (the medium-chain alcohol dehydrogenases and the short-chain dehydrogenase/reductases) are proposed to catalyze in vivo the oxidation of retinol to retinal. Although many distinct "retinol dehydrogenases" have been proposed in the literature to catalyze retinol oxidation, only a few "retinal dehydrogenases" are thought to be important in vivo for catalyzing the final oxidative step needed for retinoic acid synthesis.¹¹

The number of investigations focused on 13-*cis*-retinoic acid formation is relatively small compared with those investigations focused on all-*trans*-retinoic acid formation. However, it is generally accepted that 13-*cis*-retinoic acid can be formed in vivo through isomerization of all-*trans*-retinoic acid and possibly of 9-*cis*-retinoic acid. It is possible also that some 13-*cis*-retinoic acid is also formed in vivo through sequential oxidation of 13-*cis*-retinol.

Isomerization of all-*trans*-retinoic acid

It is now well established that 13-*cis*-retinoic acid can be formed in vivo through isomerization of all-*trans*-retinoic acid. This was originally demonstrated when radiolabeled all-*trans*-retinoic acid was administered intrajugularly to rats. The radiolabeled all-*trans*-retinoic acid was rapidly (<2 min) taken up by the intestines and other tissues. Subsequently, radiolabeled 13-*cis*-retinoic acid and uncharacterized polar metabolites appeared in the plasma.³ This indicated that all-*trans*-retinoic acid can be converted to 13-*cis*-retinoic acid within the body. Studies of cells in culture have also demonstrated that 13-*cis*-retinoic acid is formed from the all-*trans* isomer.^{5,12} Cultured rabbit tracheal epithelial cells, human umbilical cord endothelial cells, and human HepG2 hepatocytes all have been demonstrated to convert all-*trans*-retinoic acid to 13-*cis*-retinoic acid. Moreover, many pharmacokinetic studies of all-*trans*-retinoic acid in both humans and animal models have identified 13-*cis*-retinoic acid as a product that is observed on the administration of a dose of all-*trans*-retinoic acid.^{13,14}

Relevant to the dermatologic use of retinoic acid, there also is evidence for the percutaneous absorption of 13-*cis*-retinoic acid that is generated through the photo-isomerization of topically administered all-*trans*-retinoic acid.¹⁵ Twenty-four hours after a single topical application of a 0.1% cream of all-*trans*-retinoic acid to human cadaver skin, 13-*cis*-retinoic acid was

Table I. Enzyme families and species reported to catalyze retinol oxidation and proposed to be important for retinoic acid biosynthesis

Medium-chain alcohol dehydrogenase family	
Alcohol dehydrogenase, Class I (ADH1)	
Alcohol dehydrogenase, Class II (ADH2)	
Alcohol dehydrogenase, Class IV (ADH4)	
Properties	
Soluble	
Relatively abundant	
Zinc-dependent	
40 kd subunits	
Many 1-degree and 2-degree alcohols are substrates, including hydroxy-fatty acids and steroids.	
Cellular retinol-binding protein, type I (CRBP I)-bound retinol is not a substrate for ADH1, ADH2, or ADH4.	
Short-chain dehydrogenases/reductase family	
Retinol dehydrogenase, type I (RoDH(I))	
Retinol dehydrogenase, type II (RoDH(II))	
Retinol dehydrogenase, type III (RoDH(III))	
Retinol dehydrogenase, type 4 (RoDH-4)	
cRDH	
<i>cis</i> -Retinol/3 α -hydroxysterol short-chain dehydrogenase, type I (CRAD1)	
<i>cis</i> -Retinol/3 α -hydroxysterol short-chain dehydrogenase, type II (CRAD2)	
Retinol short-chain dehydrogenase/reductase 1 (retSDR1)	
11cRDH	
Properties	
Membrane-bound or -associated	
Relatively not abundant	
Zinc-independent	
28-34 kd subunits	
Involved in steroid and prostaglandin metabolism	
Cellular retinol-binding protein, type I (CRBP I)-bound retinol is a good substrate for RoDH(I), RoDH(II), RoDH(III), and RoDH-4.	
Cellular retinaldehyde-binding protein (CralBP)-bound retinol is a substrate for 11cRDH.	

detected in samples from skin exposed to light but was virtually absent in skin samples that had been maintained in the dark. Moreover, the concentration of 13-*cis*-retinoic acid in the exposed skin sample was similar to that determined for all-*trans*-retinoic acid. Thus, 13-*cis*-retinoic acid can be absorbed through the skin after photo-isomerization of topically applied all-*trans*-retinoic acid.

Possible synthesis from all-*trans*-retinol

As can be seen from Fig 1, it is theoretically possible that 13-*cis*-retinoic acid can be formed in a manner analogous to all-*trans*-retinoic acid, through sequential oxidation of 13-*cis*-retinol and 13-*cis*-reti-

Table II. Potential physiologic and pharmacologic actions of 13-*cis*-retinoic acid

Serves as a precursor/reservoir pool for all- <i>trans</i> -retinoic acid and possibly 9- <i>cis</i> -retinoic acid
Regulatory molecule influencing retinoic acid and hydroxysteroid metabolism
Effects on cellular signal transduction pathways involving the cell surface receptor
Other novel actions independent of transcriptional regulation

nal. However, the literature that supports this possibility is relatively limited. Compared with the extensive literature on tissue levels of all-*trans*-retinol and all-*trans*-retinyl esters,¹ there presently is only very limited information available regarding the tissue concentrations of 13-*cis*-retinol or 13-*cis*-retinyl esters. It has been established that 13-*cis*-retinol is formed in a time- and protein-dependent manner when all-*trans*-retinol is incubated in the presence of cell homogenate.¹⁶ This finding supports the notion that some 13-*cis*-retinol may be formed within cells from the abundant precursor, all-*trans*-retinol. It is also established that 13-*cis*-retinyl esters are present in liver.¹⁷ Because a retinyl ester hydrolase activity that is able to hydrolyze *cis*-retinyl esters also has been demonstrated to be present in liver,¹⁸ it is likely that 13-*cis*-retinol can be formed from hepatic 13-*cis*-retinyl ester. Several enzymes that are expressed in liver and other tissues and that are able to catalyze the oxidation of 13-*cis*-retinol to 13-*cis*-retinal have been described.^{16,19-22} Thus, it would appear that 13-*cis*-retinol and enzymes able to catalyze its oxidation to 13-*cis*-retinal are localized within the same tissues. These observations provide circumstantial evidence that 13-*cis*-retinoic acid also may be formed in the body through a biosynthetic pathway that does not use all-*trans*- or 9-*cis*-retinoic acid as the immediate precursor for 13-*cis*-retinoic acid. However, this possibility will require additional research before it can be considered as established.

ACTIONS OF ENDOGENOUS 13-*CIS*-RETINOIC ACID WITHIN THE BODY

Several physiologic and pharmacologic actions that have been proposed for 13-*cis*-retinoic acid are listed in Table II. Because 13-*cis*-retinoic acid does not display a strong binding affinity that is relative to all-*trans*- and 9-*cis*-retinoic acid for members of either the retinoic acid receptor family or the retinoid X receptor family of nuclear receptors,² it is generally believed that 13-*cis*-retinoic acid can act by serving as a precursor for the more transcriptionally active retinoic acid isomers. Recent studies from several dif-

ferent laboratories have suggested that 13-*cis*-retinoic acid also may play an important regulatory role in controlling the activities of enzymes thought to be involved in retinoid, androgen, and estrogen metabolism. There also have been several recent reports that suggest retinoic acid may act through a cell surface receptor to influence cellular signal transduction pathways. **Finally, in addition to these actions, it also is possible that 13-*cis*-retinoic acid may have other, as yet unknown, actions within cells and tissues.**

Conversion to transcriptionally active retinoids

Many studies that have explored the pharmacokinetic properties of 13-*cis*-retinoic acid in humans and animal models have demonstrated that both circulating and tissue concentrations of all-*trans*-retinoic acid increase in response to administration of a dose of 13-*cis*-retinoic acid.^{11,14} On the basis of these observations and the knowledge that 13-*cis*-retinoic acid acts only weakly in transactivation assays, it is generally assumed that 1 of the functions of 13-*cis*-retinoic acid is to serve as a precursor for the formation of the transcriptionally active all-*trans* isomer.

Biochemical details concerning the isomerization of 13-*cis*-retinoic acid to all-*trans*-retinoic acid are starting to become available.^{23,24} Isomerization of 13-*cis*-retinoic acid to all-*trans*-retinoic acid occurs in the presence of rat liver microsomes, and this isomerization does not require an energy source. Conversion of 13-*cis*- or 9-*cis*-retinoic acid to all-*trans*-retinoic acid can be catalyzed by purified rat liver glutathione-S-transferase. This isomerization reaction was shown to take place independent of the presence of glutathione, which indicates that isomerization is not linked with glutathione-S-transferase activity. These observations add support to the hypothesis that 13-*cis*-retinoic acid serves as a precursor for the transcriptionally active all-*trans* isomer and provides a biochemical basis for understanding the isomerization process.

13-*cis*-retinoic acid may also serve as a precursor for 9-*cis*-retinoic acid. This possibility is supported by the observation that rat liver microsomes can catalyze the isomerization of 13-*cis*-retinoic acid to the transcriptionally active 9-*cis* isomer.^{25,26} Thus, it would appear that rat liver microsomes can generate 9-*cis*-retinoic acid through isomerization of 13-*cis*-retinoic acid; consequently, it is possible that some of the physiologic actions of 13-*cis*-retinoic acid may be mediated by 9-*cis*-retinoic acid.

Possible role of 13-*cis*-retinoic acid as a regulatory molecule

There is a growing body of evidence that suggests 13-*cis*-retinoic acid acts as a potent inhibitor of the

enzyme reactions needed for retinoic acid and hydroxysteroid biosynthesis. Recent reports that implicate 13-*cis*-retinoic acid as an inhibitor of retinoid and hydroxysteroid metabolism are summarized in Table III. Among these reports, the inhibitory actions of 13-*cis*-retinoic acid on human *cis*-retinol dehydrogenase (cRDH) catalyzed oxidation of 9-*cis*-retinol to 9-*cis*-retinal, a first oxidative step needed for 9-*cis*-retinoic acid formation, are most striking. The concentration that inhibits enzyme activity by 50% (K_i) of 13-*cis*-retinoic acid on this oxidation reaction (that is, the concentration of 13-*cis*-retinoic acid that results in 50% inhibition of the enzyme's activity) is reported to be 0.1 $\mu\text{mol/L}$.¹⁶ As is recounted earlier, on the consumption of a meal of fried liver, plasma 13-*cis*-retinoic acid concentrations reach a level of approximately 0.08 $\mu\text{mol/L}$, a level approaching that needed to inhibit 50% of human cRDH activity. Hence, it would appear that fluctuations in 13-*cis*-retinoic acid concentration in the blood that can be encountered under normal physiologic circumstances may have a marked influence on cRDH activity and possibly 9-*cis*-retinoic acid formation. Interestingly, for human cRDH, the inhibitory actions of 13-*cis*-retinoic acid are quite specific, because the K_i values for all-*trans*- and 9-*cis*-retinoic acid indicate that these retinoids are approximately 20 times less potent inhibitors of human cRDH activity than 13-*cis*-retinoic acid.¹⁶ Pharmacologic administration of 13-*cis*-retinoic acid gives rise to circulating and tissue concentrations of 13-*cis*-retinoic acid that can reach the low micromolar range.^{13,14} Consequently, on the pharmacologic administration of 13-*cis*-retinoic acid, it is likely that the activities of enzymes like alcohol dehydrogenase, Class IV (which may be needed for all-*trans*-retinoic acid formation) or 17 β -hydroxysteroid dehydrogenase (which plays a role in both androgen and estrogen metabolism) will be inactivated by 13-*cis*-retinoic acid (Table III). Thus, it would seem that 13-*cis*-retinoic acid can function as a modulator of several key enzymes that are involved in retinoid and hydroxysteroid metabolism. Such actions by 13-*cis*-retinoic acid could account, in part, for why the biologic actions of 13-*cis*-retinoic acid administration are not fully duplicated by all-*trans*- and/or 9-*cis*-retinoic acid administration.

Actions of retinoic acid that involve a cell surface receptor

On the basis of the properties of all-*trans*-retinoic acid, a cell surface receptor for all-*trans*-retinoic acid would not be needed to bring about internalization of circulating retinoic acid.^{27,28} Nevertheless, it has been demonstrated that all-*trans*-retinoic acid does

Table III. Summary of recent literature reports of 13-*cis*-retinoic acid acting as an inhibitor of "retinol dehydrogenases" or hydroxysteroid dehydrogenases

Competitively inhibits retinol oxidation by human ADH4, $K_i = 3 \mu\text{mol/L}$ ³⁵
Competitively inhibits retinol oxidation by rat RoDH(I), $K_i = 12 \mu\text{mol/L}$ ³⁶
Competitively inhibits retinol oxidation by human RoDH(I), $K_i = 30 \mu\text{mol/L}$ ³⁶
Competitively inhibits 9- <i>cis</i> -retinol oxidation by human 9cRDH, $K_i = 0.1 \mu\text{mol/L}$ ¹⁶
Competitively inhibits human 17 β -hydroxysteroid dehydrogenase type 6 isozyme (liver and prostate), $K_i = 4 \mu\text{mol/L}$ ³⁶
Does not inhibit human sebaceous gland 17 β -hydroxysteroid dehydrogenase type 2 isozyme ³⁷

bind the mannose-6-phosphate/insulin-like growth factor-II receptor that is present on the plasma membranes of rat cardiac myocytes.^{29,30} It appears that binding of all-*trans*-retinoic acid to this membrane receptor may be important for the modulation of the activity of cellular signal transduction pathways and cellular activities and not for the facilitation of the uptake of all-*trans*-retinoic acid from the circulation. Although this work has focused on the actions of all-*trans*-retinoic acid in stimulating the mannose-6-phosphate/insulin-like growth factor-II receptor, the work does raise an intriguing question as to whether 13-*cis*-retinoic acid may act through similar mechanisms at the cell surface. Thus, all-*trans*- and 13-*cis*-retinoic acid may be able to influence cellular signaling pathways in a manner that is independent of the transactivational activity of retinoids. Because the published work in this area is new and the characterizations of these effects by both all-*trans*- and 13-*cis*-retinoic acid are still limited, one must be cautious about the possible global significance of these exciting findings. However, one must also recognize that the actions of 13-*cis*-retinoic acid at the level of the cell membrane might help serve to explain why 13-*cis*-retinoic acid can have effects that are independent of those effects of the all-*trans* isomer.

SUBSEQUENT METABOLISM OF 13-CIS-RETINOIC ACID ON PHARMACOLOGIC ADMINISTRATION

Like all-*trans*- and 9-*cis*-retinoic acid, 13-*cis*-retinoic acid undergoes both oxidative and conjugative metabolism. Although it is likely that most of this subsequent metabolism of the retinoic acid isomers is inactivating or catabolic in nature, some of this metabolism must also be activating because some metabolites display transactivational activity. Nevertheless,

this metabolism is worthy of brief mention because some metabolites of 13-*cis*-retinoic acid may have distinct actions within cells and tissues.

The major circulating metabolite of 13-*cis*-retinoic acid that has been observed in volunteers who receive chronic treatment with 13-*cis*-retinoic acid for dermatologic disorders has been identified to be 13-*cis*-4-oxo-retinoic acid.³¹ The next most abundant metabolite was shown to be all-*trans*-4-oxo-retinoic acid. The biliary metabolites of 13-*cis*-retinoic acid were investigated in 2 patients with biliary T-tube drainage after the administration of a single oral 80-mg dose of 13-*cis*-[¹⁴C]retinoic acid.³² Radioactivity measurements showed that the 2 patients excreted 22.7% and 17.1% of the dose in their bile within 4 days. Analysis of extracted bile samples indicated that the β -glucuronide metabolites of 13-*cis*-retinoic acid accounted for about 48% and 44% of the total radioactivity in the bile of the 2 patients. The 2 major glucuronide conjugates present in the bile were those of 13-*cis*-4-oxo-retinoic acid and 13-*cis*-16-hydroxy-retinoic acid. Relatively minor amounts of the glucuronide conjugates of unmodified 13-*cis*-retinoic acid and 13-*cis*-18-hydroxy-retinoic acid were reported to be present in bile collected from these 2 patients. The β -glucuronides of both all-*trans*- and 13-*cis*-retinoic acid are found in the circulation of healthy human volunteers after repeated administration of a dose of 13-*cis*-retinoic acid.³³

The pharmacokinetics, the blood concentrations, and urinary, biliary, and fecal excretion of 13-*cis*-[¹⁴C]retinoic acid were also studied in 4 healthy male volunteers after a single 80-mg oral dose.³⁴ Approximately 80% of the dose was recovered as radioactivity in excreta during the course of the study, with about equal fractions present in the urine and feces. A secondary peak in blood concentrations for radioactivity was observed in the healthy subjects, which suggests possible enterohepatic circulation of 13-*cis*-retinoic acid. The mean half-life for 13-*cis*-retinoic acid in the blood was 13.6 hours, whereas the corresponding value for the ¹⁴C counts per minute was 90 hours.

These pharmacokinetic studies establish that 13-*cis*-4-oxo-retinoic acid, all-*trans*-retinoic acid, and the β -glucuronide metabolites of 13-*cis*-, 13-*cis*-4-oxo-, and all-*trans*-retinoic acid represent the major metabolites of 13-*cis*-retinoic acid after its pharmacologic administration. Thus, when considering the physiologic and pharmacologic actions of 13-*cis*-retinoic acid, one must recognize that some metabolites may have distinct biologic actions that contribute to the overall biologic activity of 13-*cis*-retinoic acid.

SUMMARY AND FUTURE RESEARCH DIRECTIONS

It is accepted that 13-*cis*-retinoic acid is a naturally occurring retinoid that can be formed on the isomerization of all-*trans*-retinoic acid and possibly through sequential oxidation of 13-*cis*-retinol and 13-*cis*-retinal. We still do not understand fully how 13-*cis*-retinoic acid acts physiologically within the body. This is because 13-*cis*-retinoic acid has only relatively weak transactivational activity compared with all-*trans*- and 9-*cis*-retinoic acid, yet its biologic actions cannot be fully replicated on its substitution with either or both of these highly transcriptionally active retinoic acid isomers. Thus, 13-*cis*-retinoic acid appears to have some actions that are independent of those of the all-*trans* and 9-*cis* isomers. The recent literature suggests that 13-*cis*-retinoic acid may act both within cells as a regulatory molecule for regulating enzymes proposed to be important for catalyzing retinoic acid formation and hydroxysteroid metabolism and on the cell surface to influence the actions of membrane receptors that are importantly linked to cellular signal transduction pathways. However, the data supporting these potential actions of 13-*cis*-retinoic acid are still new and have not yet undergone the rigorous scientific scrutiny that will be needed to establish the validity of these possible actions of 13-*cis*-retinoic acid. Because 13-*cis*-retinoic acid is a very effective pharmacologic agent, there is indeed a significant need to understand fully its actions within the body. Only when full knowledge of the physiologic and pharmacologic actions of 13-*cis*-retinoic acid becomes available will its clinical use in dermatology and other branches of medicine be optimized.

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