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Retinoic acid induces expression of PA-FABP (psoriasis-associated fatty acid-binding protein) gene in human skin *in vivo* but not in cultured skin cells

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Abstract: PA-FABP (psoriasis-associated fatty acid-binding protein) is a new member of a group of low-molecular-weight proteins that are highly up-regulated in psoriatic skin and that share similarity to fatty acid-binding proteins. In this study we demonstrate that PA-FABP transcripts are expressed in human skin *in vivo* and that topical application of 0.05% retinoic acid (RA) cream results in a rapid induction of PA-FABP transcripts following treatment for 16 hours and persists at increasing levels after 48 and 96 h of RA treatment. The PA-FABP mRNA response to RA was reduced by approximately 50% when patients concurrently were treated with RA and 0.025% clobetasol propionate (CLO) for 48 and 96 h, whereas treatment with CLO alone resulted in PA-FABP transcript levels not significantly different from vehicle-treated skin. When comparing the effects of a well-known irritant, sodium lauryl sulfate (SLS), to those of RA and its vehicle, 0.05% RA cream but not 2% SLS in RA vehicle caused PA-FABP mRNA induction after 16 h. SLS treatment of human skin for 96 h caused a slight increase in PA-FABP transcripts, but markedly less than that observed in response to RA treatment. Incubation of cultured human keratinocytes or skin fibroblasts with RA for up to 48 h did not significantly induce PA-FABP transcripts. Expression of PA-FABP message in keratinocytes was observed to be induced by calcium and fetal calf serum (FCS), while tetra-decanoyl phorbol acetate (TPA) caused little or no induction. Taken together, the marked inducibility of the PA-FABP gene is compatible with the possibility that this gene might be important in RA-mediated regulation of human skin growth and differentiation.

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Introduction

The fatty acid-binding proteins (FABPs) belong to a multigene family of low molecular weight cytoplasmic binding proteins (≈14–15 kDa) that bind fatty acids, and are abundantly expressed in tissues specialized in the synthesis, transport, storage and utilization of fatty acids. Their putative main physiological significance is the assurance that long-chain fatty acids and derivatives, either in transit through membranes or present in intracellular compartments, are largely complexed to proteins (1). Also, since recent data indicate the involvement of fatty acids and fatty acid derivatives (e.g., eicosanoids) in cellular growth and differentiation and signal transduction pathways, their respective binding proteins may also function in these complex processes (2, 3).

The epidermis is a specialized tissue of lipid metabolism, but cannot synthezise some of the fatty acids (i.e., linoleic acid, arachidonic acid) that are important for epidermal growth and barrier functions (4). Thus, fatty acid transport in the skin and its metabolism may be facilitated by FABPs. In

fractionated non-cultured psoriatic keratinocytes there is evidence of an altered fatty acid transport and metabolism which is in line with the dramatic up-regulation of a group of FABPs including psoriasin, calgranulin A and B, and cystatin A (5, 6). Recently, Madsen et al. (7) identified a new member of this group that is highly up-regulated at the message and protein levels in non-cultured psoriatic keratinocytes and termed it PA-FABP (psoriasis-associated fatty acid-binding protein). However, nothing is known about PA-FABP gene expression and regulation in human skin. The main purpose of the present study was to examine the regulation of PA-FABP gene expression in human skin *in vivo* as well as in cultured skin cells. Since topical retinoic acid can cause an erythematous reaction clinically similar to irritant dermatitis (8–10), an important issue is the extent to which alterations induced by RA are caused by its irritant properties or by more physiologically relevant mechanisms. Therefore, we have also examined the effects of the irritant sodium lauryl sulfate (SLS) as well as the anti-inflammatory compound clobetasol propionate (CLO) on expression of PA-FABP.

Material and methods

Polymerase chain reaction (PCR) and cDNA cloning

PCR was carried out in an automated Perkin-Elmer Cetus thermocycler using 1 µg of total RNA extracted from keratome biopsies of psoriatic skin. RNA was reverse transcribed into a complementary DNA using reverse transcriptase (2.5 U) and oligo d(T)16 as primers (2.5 µM), at 42°C for 25 min, in a total volume of 20 µl buffer (5 mM $MgCl_2$, 1×reaction buffer as supplied by the manufacturer, 1 mM dXTP, 1 mM RNase inhibitor) overlaid with 70 µl of mineral oil (Gene Amp. RNA Kit, Perkin Elmer Cetus, CT, USA). Thirty-five cycles of PCR amplification (95°C, 1 min, 50°C, 1 min, 72°C, 1 min) were performed in 100 µl using Ampli Taq DNA polymerase (2.5 U), 2.6 mM $MgCl_2$, 1×reaction buffer, and 0.15 µM (final concentration) of each primer as suggested by the manufacturer. The oligonucleotide primers were synthesized by the University of Michigan DNA core facility and based upon a previously published cDNA sequence (7). Each primer had 25 nucleotides hybridizing to its template and at its 5′-end, a restriction site and 6 additional nucleotides that facilitate complete digestion with the restriction enzymes. Eco RI and Bam HI sites were contained in the forward and reverse primers, respectively. The primers were designed so as to amplify the coding region and were as follows:

Forward: 5′-gtttcc**gaattc**ACCGCCGACGCAGACCCCTCTCTGC-3′
Reverse: 5′-caaacc**ggatcc**GGGATGATCCTAATTAATCCAACAC-3′

The length of the amplified DNA was determined on a 1.5% agarose gel. The amplified 633-bp region of PA-FABP was isolated from the gel, ethanol precipitated and subcloned into plasmid pSG5 (Stratagene, La Jolla, CA, USA).

Skin biopsies

For *in vivo* treatment, 0.05% retinoic acid cream, its vehicle (Ortho Pharmaceuticals, Raritan, NJ, USA) or 0.025% clobetasol propionate (CLO) ointment (Glaxo Dermatology, NC, USA) was applied once as 3×9 cm patches to buttock skin and maintained under plastic wrap for 24, 48, or 96 h prior to biopsy. When patients concurrently were treated with RA and CLO equal amounts of 0.1% RA and 0.05% CLO (approximately 250 mg of each) were mixed and applied to the skin. Subjects were also treated for 16 or 96 h under occlusion with 2% SLS. SLS was obtained from E.I. Dupont De Nemours & Company (Wilmington, DE, USA) and compounded at 2% in RA vehicle cream. After obtaining written informed consent, keratome biopsies consisting primarily of epidermis (11) were procured from the treated areas using 1% plain lidocaine as a local anesthetic. Epidermal keratomes were immediately frozen in liquid nitrogen and stored at −70°C until use. All subjects provided written, informed consent and all procedures were performed under approval of the University of Michigan Medical Center Institutional Review Board.

Cell culture

Human keratinocytes were purchased from Clonetics and expanded to about 50% confluency in 150-mm tissue culture dishes in a low Ca^{++} (0.15 mM), serum-free keratinocyte growth medium (KGM) containing epidermal growth factor (EGF) (0.1 ng/ml), insulin (5 µg/ml), hydrocortisone (0.5 µg/ml), bovine pituitary extract, gentamicin (50 µg/ml), and amphotericin-B (50 ng/ml) (Clonetics, San Diego, CA, USA). The effect of glucocorticoid was examined after the medium was replaced with hydrocortisone-free KGM medium 48 h prior to treatment. Cells were treated up to 48 h with 1 µM RA or calcium (2 mM) or with FCS (10%) or TPA (20 nM).

Human dermal fibroblasts were also used in this study. They were prepared from punch biopsies of buttock skin (12) and propagated in Dulbecco's

modified Eagle's medium containing 10% fetal calf serum (FCS), 100 U/ml of penicillin, and 100 µg/ml of streptomycin. Cells were then grown to confluency in 150-mm tissue culture dishes (Corning Glass Co., Corning, NY, USA) and treated for up to 48 h.

Cells were maintained in a humidified incubator at 37°C with 5% CO_2/95% air. When cells were treated with RA, they were protected from light during the incubation period. Experiments were conducted on cells in the third through sixth passage.

Northern analysis of mRNA

RNA was isolated from cultured human skin fibroblasts, keratinocytes or frozen keratome biopsies by guanidinium isothiocyanate lysis and ultracentrifugation as previously described (13). Briefly, RNA concentrations were determined by absorbance at 260 nm and equal quantities of total RNA were electrophoretically separated in 1% formaldehyde-agarose gels containing 0.5 µg/ml ethidium bromide. Twenty micrograms total RNA was transferred to derivatized nylon membranes (Zeta-Probe, Bio-Rad, Richmond, CA, USA). Filters were baked 2 h at 80°C *in vacuo*, then prehybridized for 2–4 h at 42°C in 50% formamide, 5×SSC (1×SSC=150 mM NaCl, 15 mM sodium citrate), 50 mM sodium phosphate, pH 7.0, 1×Denhardt's solution, 250 µg/ml yeast tRNA, 100 µg/ml sonicated herring sperm DNA, and 1% SDS. Hybridization was carried out for 18 h at 42°C in the same buffer. Blots were sequentially hybridized against ^{32}P-labeled PA-FABP and cyclophilin (14) probes prepared by random priming. Quantitation of mRNA levels was performed using a phosphorimager (Molecular Dynamics, Sunnyvale, CA, USA), and PA-FABP message levels were normalized to cyclophilin. Filters were washed once in 0.2×SSC, 0.1% SDS at room temperature, then twice for 15 min in 0.2×SSC, 0.1% SDS at 56°C and finally once for 15 min in 0.1×SSC, 0.1% SDS also at 56°C. An adult Multiple Tissue Northern Blot was purchased from Clontech Lab., Inc. and contained 2 µg in each lane of highly pure poly (A)$^+$RNA from 8 different tissues. Autoradiography was performed using intensifying screens at −70°C.

Statistics

For each duration of time (i.e. 16, 24, 48, and 96 h) the -fold induction was compared to unity by a one-sample t-test. All p-values are two-tailed.

Results

Expression of PA-FABP mRNA in human skin in vivo

PA-FABP transcripts were detectable in untreated skin (data not shown) as well as skin treated with vehicle (Fig. 1). As shown in Fig. 1, PA-FABP mRNA was markedly and significantly increased by RA treatment compared to vehicle-treated skin at all time points studied (24, 48, and 96 h). Induction was observed as early as 16 h after topical RA treatment (mean 2.0-fold±0.23 SEM, p=0.006, n=7) (data not shown) with increasing values following treatment for 24 h (mean 2.8-fold±0.34 SEM, p=0.006), 48 h (mean 8.2-fold±2.5 SEM, p=0.04), and 96 h (mean 17.3-fold±5.5 SEM, p=0.03). However, a considerable inter-individual variation in -fold induction existed both at 48 (range 3 to 18) and 96 h (range 5 to 34). At these time points the induction of PA-FABP mRNA by RA was reduced by approximately 50% when patients concurrently were treated with RA and CLO. Treatment with CLO alone resulted in PA-FABP transcript levels not significantly different from vehicle-treated skin.

The treatment sites were assessed for erythema

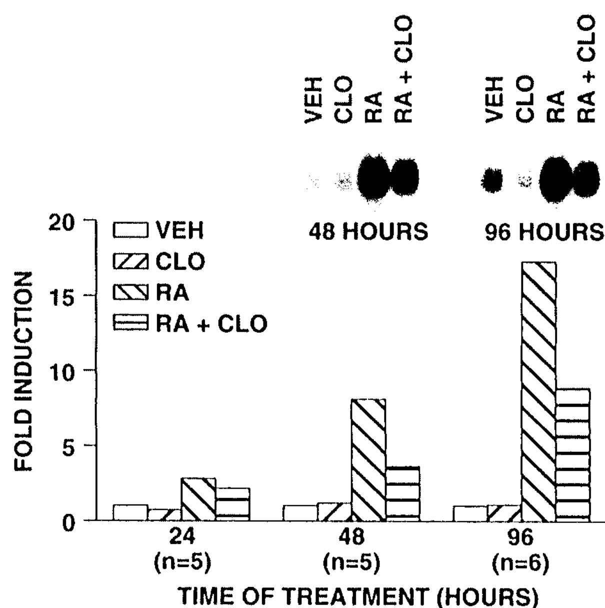

Figure 1. a) Induction of PA-FABP mRNA in human skin by topically applied retinoic acid cream (RA). Each volunteer was treated with 0.05% RA, its vehicle, 0.025% clobetasol propionate ointment (CLO), or RA and CLO in combination under occlusion for the times indicated prior to biopsy. *n* is the number of RA, CLO or RA/CLO treated patients obtained at each time point. *b)* autoradiographic bands from two representative experiments following treatment for 48 and 96 h.

using a 0–9 scale, 0 representing absent, and 9 maximal erythema (10). However, there was no correlation between degree of erythema and -fold induction by RA.

Effect of sodium lauryl sulfate on PA-FABP expression in human skin in vivo

The above data clearly demonstrate that PA-FABP expression is increased in skin treated with topical RA. To determine whether this response was specific to RA, biopsies were obtained from subjects treated with the irritant sodium lauryl sulfate (SLS) prepared in retinoic acid vehicle for 16 or 96 h under occlusion. Both 2% SDS and 0.05% RA produced a marked increase in erythema relative to vehicle after 96 h, which was comparable between the two agents. Little or no erythema was observed in response to vehicle after 96 h, nor to any of the treatments after 16 h. In 7 patients treated with SLS or RA cream for 16 h, PA-FABP transcripts were not significantly induced compared to vehicle following SLS treatment (mean 0.96-fold±0.06, $p=0.54$), while as mentioned above RA treatment resulted in a significant induction. Also, the induction of PA-FABP mRNA by SLS after treatment for 96 h was markedly less than that obtained in response to RA (Fig. 2).

Expression of PA-FABP in human keratinocytes and fibroblasts

Because RA induced PA-FABP mRNA *in vivo*, it was of interest to determine whether an induction also occurred in cultured human keratinocytes. Subconfluent cultures of keratinocytes were harvested, RNA extracted, and PA-FABP mRNA levels were determined. In untreated keratinocytes, PA-FABP mRNA was at a low but detectable level. Treatment of keratinocytes by RA for 24 or 48 h did not induce PA-FABP mRNA when cells were grown in the presence or absence of hydrocortisone (Fig. 3). When grown in the presence of hydrocortisone, markedly lower transcript levels were observed in both unstimulated (control) and stimulated cells. Treatment with calcium for 48 h resulted in an approximately 2-fold induction of PA-FABP transcripts. In a separate experiment, incubation of keratinocytes with FCS (10%) for 48 h also induced PA-FABP gene expression (≈3-fold), while TPA (20 nM) had little or no inducible effect (data not shown). Induction of PA-FABP expression by RA was also determined in fibroblasts. In these cells, transcripts were undetectable both in untreated cells and in cells after treatment with RA (1 μM) for 24 and 48 h (data not shown).

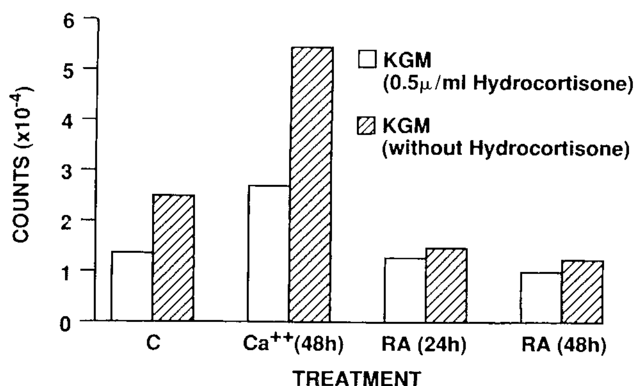

Figure 3. Induction of PA-FABP mRNA by calcium (Ca^{++}) (2 mM) and retinoic acid (RA) (1 μM) in normal adult human keratinocytes. When cells were 50% confluent, they were either maintained in hydrocortisone-containing KGM (Clonetics) growth media or the media were replaced with hydrocortisone-free KGM media 48 h prior to Ca^{++} or RA treatment.

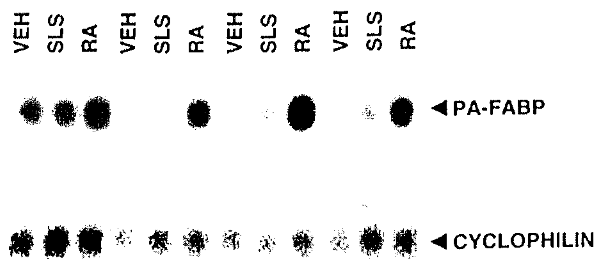

Figure 2. Induction of PA-FABP mRNA in human skin by topically applied sodium lauryl sulfate (SLS) or retinoic acid cream (RA). Four individuals were treated for 96 h under occlusion with vehicle (V), 2% SLS, or 0.05% RA. Total RNA (20 μg per lane) was successively filter hybridized with ^{32}P-labeled cDNA probes for PA-FABP and cyclophilin.

Presence of PA-FABP mRNA in adult human tissues

To determine the tissue distribution of PA-FABP gene expression, poly(A)$^+$RNA from various adult human tissues was analyzed (Fig. 4). Of the tissues examined, heart and placenta had a high level of PA-FABP mRNA, while brain, lung, skeletal muscle and pancreas had moderate levels. In liver and kidney tissue levels of PA-FABP transcripts were not detectable.

Discussion

Low-molecular-weight FABPs are abundant (i.e., 1–2% of cytosolic protein) in tissues that are active

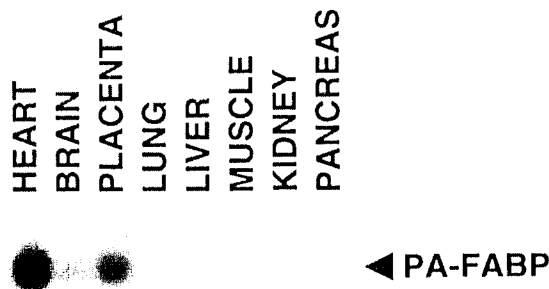

Figure 4. Expression of basal PA-FABP mRNA levels in various adult human tissues.

in fatty acid synthesis, transport, storage, or utilization (15, 16). Whereas the lipid metabolic activity might predict the presence of cytosolic FABPs in epidermis, available data are conflicting. Thus, Schurer et al. (17) found that cytosol from epidermis *in vivo* and *in vitro* showed no fatty acid binding activity within the molecular weight range (12–14 kDa) of these conventional FABPs. However, Siegenthaler et al. (18) characterized an E-FABP (15 kDa) in human epidermal cells that binds oleic acid with high affinity but does not bind all-trans-, 13-cis- and 9-cis-retinoic acid nor all-trans-retinol. They also showed that expression levels of E-FABP were low in normal epidermis, higher in human cultured keratinocytes and still higher in psoriasis. Recently, Madsen et al. (7) also identified a protein (PA-FABP) with homology to other members of the FABP family, that was highly up-regulated in psoriatic skin. Whether PA-FABP and E-FABP are the same or different proteins remains to be investigated.

We have previously cloned and investigated the regulation of a human retinoic acid binding protein (CRABP-II), which is a member of the hydrophobic ligand binding family of proteins that includes FABPs and CRBPs (13, 19, 20). It has been shown that CRABP-II is highly inducible by RA and is also overexpressed in psoriasis (13, 19–21). For this reason we determined whether PA-FABP also was regulated by RA. Interestingly, PA-FABP mRNA was induced following RA treatment for 16 h, whereas no induction was observed, compared to vehicle-treated skin, following SLS treatment for the same period of time. Despite the induction of marked erythema by both SLS and RA after treatment for 96 h, the induction of PA-FABP mRNA by SLS was markedly less than that obtained in response to RA (Fig. 2). It has previously been shown that SLS and RA elicit a similar clinical and histologic response following treatment for 96 h (9). Also, a time-course comparison demonstrated that RA induced epidermal thickening, stratum corneum compaction, spongiosis, and mitotic figures more rapidly than did SLS (22). Taken together, these findings indicate differing mechanisms of actions of the two agents, and that the PA-FABP mRNA induction by RA in human skin *in vivo* cannot be accounted for by irritant effects. A similar effect of RA and SLS on CRABP-II mRNA levels in human skin *in vivo* has also been demonstrated (10).

Glucocorticoids are effective for the treatment of various inflammatory skin diseases including psoriasis. Retinoids exert an opposite effect compared to glucocorticoids and cause hyperplasia of the skin when applied topically (9, 22). It has been shown that retinoids can reverse glucocorticoid-induced atrophy in humans and mice, while the anti-inflammatory property of glucocorticoids is not affected (23, 24). It was therefore of interest to investigate the effects of glucocorticoids on PA-FABP expression. We found that CLO opposed the effect of RA-induced PA-FABP expression in human skin *in vivo* (Fig. 1). Whether this effect of CLO on PA-FABP expression is due to a direct down-regulation of the gene by the glucocorticoid receptor or is a secondary effect remains to be investigated. It was, however, clear from the *in vitro* experiment that PA-FABP transcripts were markedly lower in both unstimulated and stimulated keratinocytes when grown in the presence of hydrocortisone, which favors the possibility that glucocorticoids directly down-regulate the PA-FABP gene (Fig. 3).

Exposure of keratinizing cells to retinoids has been shown to inhibit the normal sequence of keratin expression (25) and cornified envelope formation (26). The extent of keratinocyte differentiation can be enhanced under submerged conditions, when the keratinocytes are cultured in the presence of delipidized serum to reduce the level of RA (25). Furthermore, addition of RA at micromolar concentrations to submerged cultures grown in RA-depleted medium induces marked changes in lipid synthesis and lipid composition with a decreased cholesterol sulfate production (27) and leads to a complete suppression of acylceramide and lanosterol synthesis (28). Our findings that treatment of subconfluent cultures of keratinocytes with RA for up to 48 h showed unaltered or a tendency towards decreased PA-FABP mRNA levels as compared with basic levels might thus possibly reflect an altered lipid metabolism (Fig. 3). In contrast to RA, when grown at physiological calcium concentrations, keratinocytes display a markedly higher capacity to differentiate. Also, both involucrin content and transglutaminase activity, two key determinants of cornified en-

velope during terminal differentiation, are accelerated and begin to occur prior to confluence when the extracellular calcium concentrations are raised to physiological levels (29). PA-FABP mRNA was found to respond to both external calcium (2 mM) (Fig. 3) and FCS (10%) (data not shown) which favors the concept that the stratified structure of the epidermis and/or the presence of dermis is an important determinant of PA-FABP regulation *in vivo*. Taken together, our findings are in accordance to those of Madsen et al. (7) who found that, under conditions that promoted incomplete terminal differentiation (10% FCS), PA-FABP and a few other proteins were strongly up-regulated.

Although the FABPs have functional similarities, their amino acid sequences are unique for each tissue type; but across species the FABP of a specific tissue has a highly conserved amino acid sequence. The tissues containing the most abundant quantities of the FABPs are found in liver (3% of cytosol protein), intestine (1–2% of cytosol protein), and heart muscle (5% of cytosol protein) (30). Using a PAGE-autoradioblotting technique, Siegenthaler et al. (18) demonstrated that liver-, intestine-, and heart- when compared to E-FABP showed distinct mobilities, suggesting that the primary structure of E-FABP may be different in these tissue. The study also showed that E-FABP was detectable in adipose tissues. The present study reveals that PA-FABP mRNA expression is not restricted to epidermal cells since high or moderate message levels were detected in heart, placenta, brain, lung, skeletal muscle and pancreas.

In conclusion, the main findings of the present study show that PA-FABP is regulated by RA in human skin *in vivo* but not in cultured keratinocytes or skin fibroblasts. We also demonstrate that PA-FABP mRNA induction by RA in human skin cannot be explained by its "irritant" properties since PA-FABP mRNA induction after 96 h is markedly less following topical application of the irritant SLS than that obtained in response to topical RA treatment. Although PA-FABP was named such because it is highly up-regulated in psoriatic keratinocytes the present study shows that it is simply an RA-regulated FABP found both in skin and several other tissues.

Acknowledgments

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