A Polymorphism in the Human Intestinal Fatty Acid Binding Protein Alters Fatty Acid Transport across Caco-2 Cells

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The human intestinal fatty acid binding protein (IFABP) binds long-chain fatty acids in vitro, but its intracellular function has remained speculative. A polymorphism in the gene that encodes IFABP results in an alanine (Ala) to threonine (Thr) substitution at codon 54 that alters the in vitro binding affinity of the protein for long-chain fatty acids. To identify potential functional variability between Ala and Thr IFABP, we established permanently transfected Caco-2 cell lines that express either Ala or Thr IFABP. We found that Caco-2 cells expressing Thr IFABP transport long-chain fatty acids and secrete triglycerides to a greater degree than Caco-2 cells expressing Ala IFABP. These results provide the first demonstration that IFABP participates in the intracellular transport of long-chain fatty acids. In addition, the observed increase in transport of fatty acids across cells expressing Thr IFABP suggests a plausible physiologic mechanism for our prior observation that Pima Indians with a Thr IFABP genotype have increased post-absorptive lipid oxidation rates and are more insulin-resistant than Pimas with a Ala IFABP genotype.

Long-chain free fatty acids, a major hydrolysis product of dietary triglycerides, are absorbed from the lumen into polarized enterocytes that line the small intestine. Following apical absorption into the enterocytes, free fatty acids are reincorporated into triglycerides, which are secreted basolaterally as chylomicrons. The intestinal fatty acid binding protein (IFABP) is a small (15 kDa), highly abundant protein expressed solely in enterocytes of the proximal small intestine (1). IFABP has been shown to bind both saturated and unsaturated long-chain fatty acids in vitro (2, 3). Several functions for IFABP have been proposed, which have included the facilitation of cellular uptake and/or transport of long-chain fatty acids within enterocytes (1).

We have recently reported a polymorphism in the second exon of the FABP2 gene, which encodes human IFABP (4). This A → G single base polymorphism results in an alanine (Ala) to threonine (Thr) substitution at amino acid 54 (codon 55).

Our genetic studies with Pima Indians, a population with a high prevalence of obesity, insulin resistance, and non-insulin-dependent diabetes mellitus, have shown that the Thr encoding IFABP genotype (frequency = 0.29) is associated with increased fasting lipid oxidation rates and insulin resistance (4). We further reported that recombinant Thr protein has a 2-fold higher affinity for long-chain fatty acids in vitro as compared to recombinant Ala protein (4).

The crystal structure of rat IFABP, which has high sequence homology to the human IFABP, has been determined (5). The major conformational adjustment between the structure of IFABP alone and the structure of IFABP bound to fatty acid occurs at a tight turn containing residues 54 and 55. These residues shift in position when long-chain fatty acids are bound to the protein. Therefore, even a subtle change in the amino acid sequence of this turn could affect the structural properties of IFABP in such a way as to alter its ligand affinity. Since the alanine to threonine substitution at residue 54 is part of this critical turn, it is not surprising that the two forms of this protein have different affinities for long-chain fatty acids. It is also possible that this substitution could affect the kinetics of fatty acid acquisition/release to cytoplasm, transport of fatty acids across the cell, or trafficking of fatty acids to metabolic pathways within the cell.

To determine whether the Ala → Thr substitution in IFABP alters the rate of intracellular fatty acid transport, we analyzed fatty acid transport across intestine-like cultured cells expressing either Ala or Thr IFABP. Caco-2 cells provided a model system for analysis of lipid trafficking since these cells mimic the small intestinal epithelium, are capable of absorbing long-chain fatty acids and secreting chylomicrons, and do not endogenously express IFABP (6-12). Introduction of Ala and Thr IFABP into Caco-2 cells allowed direct assessment of the effect of this single amino acid substitution on the rate of intracellular fatty acid transport and triglyceride release, which could potentially contribute to the development of insulin resistance.

EXPERIMENTAL PROCEDURES

Cell Culture—The human colonic carcinoma cell line Caco-2 was obtained from the American Type Culture Collection. Cells were cultured in Dulbecco’s modified Eagle’s medium supplemented with 2 mM glutamine, 0.1 mM nonessential amino acids, 20% fetal bovine serum, and 100 μg/ml penicillin/streptomycin.

Expression Vector Construction—Human Ala IFABP cDNA was obtained by reverse transcription/PCR amplification of jejunal mRNA, and Thr IFABP cDNA was produced by site-directed mutagenesis as described previously (4). The cDNAs were ligated into the expression vector pRC/RSV (Invitrogen), which contains the neomycin gene.

Cell Transformation—A calcium phosphate transfection system (Life Technologies) was used to transform Caco-2 cells with pRC/RSV-IFABP expression plasmids. Transformants were selected by incubation in medium containing 200 μg/ml G418.プ

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CellTransformation—

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Technologies, Inc.) was used for production of stably transfected cell lines. Caco-2 cells were plated at 1 x 10^6 cells/100-mm dish and transfected with 20 μg of DNA 1 day post-plating. Cells and DNA were cocultivated for 18 h, the DNA was removed, and the cells were incubated with fresh medium for 24 h. Forty-eight hours post-transfection, the cells were split 1:10, 1:100, and 1:1,000 in media containing G418 sulfate (500 μg/ml) and plated onto 60-mm dishes. After 3 days in selection media for 21 days, independent G418-resistant cell foci were isolated with donning rings and the cells were expanded.

Maintenance of Transfected and Non-transfected Cell Lines—Transfected cell lines were maintained in media containing G418 sulfate (500 μg/ml). Cell lines that did not demonstrate a steady rate of proliferation were discarded. Five transfected cell lines exhibited identical rates of proliferation. To best maintain a constant "identity" and stage of maturation for these transfected cell lines, as well as non-transfected Caco-2 cells, all cells were maintained under identical conditions. Stocks were frozen and thawed simultaneously, the lines were passaged Caco-2 cells, all cells were maintained under identical conditions. Stocks were frozen and thawed simultaneously, the lines were passaged as needed.

Detection of IFABP mRNA in Permanently Transfected Caco-2 Cells—Poly(A)+ RNA was isolated from transfected cells using the MicroFast Track mRNA isolation kit (Invitrogen). The mRNA (0.5 μg) was reverse-transcribed using an oligo(dT)18 primer under the conditions of the first strand cDNA synthesis reaction (Clontech). The 3-end (300 base pairs) of IFABP cDNA was specifically amplified by PCR. For each reaction, 5 μl of cDNA was amplified for 25 cycles. Amplified DNA was separated through a 2% agarose gel and visualized by ethidium bromide staining. The size of the amplified fragment corresponded to an amplification of cDNA rather than genomic DNA.

Western Blot Analysis of Transfected Cell Lysates—Permanently transfected Caco-2 cells that exhibited similar rates of growth were harvested by scraping mature monolayers (14 days post-confluence). Pelleted cells were washed and resuspended in an Nonidet P-40 lysis buffer (20 mM HEPES pH 7.5, 120 mM KCl, 1 mM dithiothreitol, 1 mM MgOAc, 10% glycerol, 0.5% Nonidet P-40, and 1 mM benzamidine) for 20 min on ice. Cell lysates were centrifuged at 12,000 x g for 30 min at 4 °C, and the supernatants were collected. Total protein was measured using the Bio-Rad protein assay. For Western blot analysis, protein lysates were separated on 15% polyacrylamide gels by SDS-polyacrylamide gel electrophoresis and transferred onto nitrocellulose. Western blots were probed with rabbit anti-human IFABP antiserum and rabbit anti-human liver FABP (LFABP) antiserum. Blots were developed by enhanced chemiluminescence according to the manufacturer's instructions (ECL Western blotting detection system, Amersham Corp.). To determine comparative amounts of IFABP in the various permanently transfected Caco-2 cell lysates, autoradiographs were scanned with a laser densitometer (Bioimage, Ann Arbor, MI). Purified recombinant intestinal and liver FABPs were used as standards for the Western blots to establish the linearity of the densitometer's readings and the respective band intensities.

Incubation of Cells with Radiolabeled Fatty Acids—Cells were plated at a density of ~1 x 10^6 cells/cm² onto 30-mm, 0.45-μm Millicell-HA filter inserts (Millipore). The inserts were placed in six-well tissue culture plates, and 2 and 3 ml of media were added to the top (apical) and bottom (basolateral) compartments, respectively. Medium was changed daily. Cell monolayers were grown on filter supports to 14 days post-confluence to best mimic enterocytes (8–12). The tightness of the monolayers was accessed by an epithelial voltohmeter using dual "chopstick" electrodes (World Precision Instruments, New Haven, CT) (8). Tight monolayers with transepithelial resistances between 250 and 320 ohms/cm² were utilized for lipid transport studies. Each experiment contained three replicate filter inserts.

Apical and basolateral medium were replaced with serum-free medium, and cells were serum-starved for 15 h. [3H]Oleic acid-sodium taurocholate micelles were prepared by mixing 100 μM sodium salt of oleic acid (Nu-Chek Prep, Elysian, MN) and 10 μM [3H]oleic acid (Du Pont NEN) with serum-free medium containing 8 mM sodium taurocholate and incubating the solution at 37 °C for 30 min. [3H]Oleic acid-sodium taurocholate micelles were prepared by the same method. Cells were incubated with long-chain fatty acids by replacing the apical medium with 2 ml of medium containing the fatty acid-taurocholate micelles. The basolateral medium was replaced with serum-free medium containing only 8 mM sodium taurocholate. Cells were incubated with the fatty acids at 37 °C in an atmosphere of 95% air, 5% CO₂ from 5 min to 48 h. At the end of the incubation, apical and basolateral media were removed. Apical and basolateral compartments were washed with 2 ml of phosphate-buffered saline, and the wash was combined with the media. Scintillation fluid was added and the radioactivity in the basolateral media was determined by scintillation counting. Following each incubation, the monolayers were assayed for total protein to control for potential overgrowth or "pulling up" of cells. All experiments were performed with at least three filters.

Lipid Extraction—Lipids were extracted from the basolateral medium according to the method of Bligh and Dyer (13). Briefly, 1 ml of the medium was added to 3.75 ml of methanol/chloroform at 2:1 (v/v). The mixture was shaken for 30 min at 24 °C and then centrifuged (10,000 x g for 15 min). The lipid-rich supernatant was removed, and the protein pellet was resuspended in 1 ml of phosphate-buffered saline and re-extracted as above. The combined supernatants were diluted with 5 ml of chloroform/water (1:1), and 1 ml HCl was added to a final pH of 3–4. The acidified extract was centrifuged (10,000 x g for 15 min), and the chloroform layer was removed and saved. The aqueous layer was re-extracted with 2.5 ml of chloroform, and the combined chloroform extracts were evaporated under a stream of N₂. The residue was redissolved in chloroform and stored at −20 °C.

Thin-layer Chromatography—Thin-layer chromatography was used to determine the type of lipids being secreted basolaterally from the Caco-2 cells following apical exposure to [3H]oleic acid. Extracted lipid was spotted on thin-layer chromatography plates (20 cm x 20 cm, Silica Gel, Kodak) and developed in hexane-ethyl ether-acetic acid (80:20:1). Lipid standards consisting of monoglycerides, diglycerides, triglycerides, oleic acid, cholesterol, and cholesteryl oleate were included in the analysis. The plates were developed with iodine vapor. Spots were cut out, and the amount of [3H] was determined by scintillation counting.

RESULTS AND DISCUSSION

Transfection of Caco-2 cells resulted in five permanently transfected cell lines (two independent cell lines expressing Ala54 IFABP and three independent cell lines expressing Thr54 IFABP), which continually exhibited identical proliferation rates and saturation densities when maintained in media containing 500 μg/ml G418. For lipid transport studies, these cells were grown on filter supports until 14 days post-confluence to best mimic mature enterocytes (8). Tight monolayers of cells (transepithelial resistances between 250 and 320 ohms/cm²) consistently contained equivalent amounts of total protein (±10% variability). Mature, tight monolayers of cells were incubated for 1.5 h in media containing 100 μM [3H]oleic acid or [3H]palmitic acid in taurocholate micelles (11). Following each incubation, [3H]-lipid that had been transported across the transfected monolayer and secreted into the basolateral compartment was collected and the amount of [3H] was determined by scintillation counting. Two diones expressing Ala54 IFABP and three diones expressing Thr54 IFABP were analyzed for transport of 100 μM oleic acid or palmitic acid at 1.5 h. Levels of expression of IFABP for each of the transfected diones is given. The amount of radiolabeled fatty acid that was transported across confluent monolayers of these cells is given (mean ± S.D.) for three replicate filters.

| Clone | Level of IFABP expression | Oleic acid at 1.5 h | Palmitic acid at 1.5 h |
|-------|---------------------------|--------------------|-----------------------|
| Ala54 A | 127                      | 31 ± 6             | 42 ± 3                |
| Ala54 B | 123                      | 34 ± 4             | 41 ± 4                |
| Thr54 A | 123                      | 60 ± 1             | 83 ± 5                |
| Thr54 B | 83                       | 51 ± 2             | 62 ± 5                |
| Thr54 C | 50                       | 43 ± 2             | 51 ± 6                |
amplification of IFABP cDNA, and consistently produced equivalent amounts of Ala 54 or Thr 54 IFABP, as determined by quantification of the 15-kDa IFABP immunoreactive band on three occasions over the period of several months (Fig. 1). Therefore, these two clones were compared in all further studies.

Transfected cells were incubated for 3.5, 24, or 48 h in media containing [3H]oleic acid or [3H]palmitic acid in taurocholate micelles. At all time points, and with both the saturated (palmitic acid) and unsaturated (oleic acid) fatty acids, approximately twice as much [3H]-lipid was apically to basolaterally transported across the Thr 54 cells as compared to the Ala 54 cells (Fig. 2, A and B). The difference in rate of apical to basolateral transport of long-chain fatty acid across the Ala 54 and Thr 54 cells appears to be specific for molecules that interact with IFABP, since no difference in [14C]glucose transport was observed in these cells (Fig. 2 C). This increase in lipid transport was not due to an increased level of endogenously expressed LFABP in the Thr 54-expressing Caco-2 cells, as LFABP may also contribute to the total transport of long-chain fatty acids. However, Caco-2 cells expressing either Ala 54 or Thr 54 IFABP were found to produce lower levels of LFABP than non-transfected Caco-2 cells. Lower levels of LFABP, a maturation-dependent protein, were observed in transfected cells at both 4 days and 14 days post-confluence, when compared to non-transfected cells (Fig. 3 and Table II), which suggests a co-regulation between the intestinal and liver forms of this protein. Since LFABP was more abundant in the non-transfected cells than comparatively mature IFABP transfected cells, non-transfected cells did not provide a "baseline" control for lipid transport by IFABP in these experiments (Fig. 4). The contribution of LFABP to total transport in the IFABP transfected cells remains unclear. At 4 days post-confluence, when LFABP is barely detectable in the transfected cells, a 2-fold difference in transport across Ala 54 and Thr 54 cells is observed. At 14 days post-confluence, a similar 2-fold difference in transport is observed, despite the greater abundance of LFABP in these mature cells. These results support a mechanism whereby LFABP and IFABP do not transport in a simple ad-

**FIG. 1.** Detection of IFABP mRNA and protein in transfected Caco-2 cells from clones Ala 54 B and Thr 54 A. A, poly(A) RNA from transfected and non-transfected Caco-2 cells was reverse-transcribed. The resulting cDNA was used as a template for 25 cycles of PCR using primers that span 300 base pairs of IFABP cDNA. B, Western blot analysis of protein lysates from these clones using antiserum raised against rat IFABP. Human IFABP migrates at 15 kDa.

**FIG. 2.** Transport of [3H]-lipid and [14C]glucose across transfected Caco-2 cells from clones Ala 54 B and Thr 54 A. Panel A, apical exposure of the cells to 100 μM of [3H]oleic acid (specific activity 1 nmol/83,000 dpm) in sodium taurocholate micelles. Cells were incubated for 3.5 and 24 h, and the basolateral medium was analyzed for [3H]. At each time point, three or four replicate filters were analyzed for each cell type. The mean ± S.D. is given for three separate experiments. Panel B, apical exposure of the cells to 100 μM [3H]palmitic acid (specific activity 1 nmol/83,000 dpm) in sodium taurocholate micelles. Cells were incubated for 24 and 48 h, and the basolateral medium was analyzed for [3H]. At each time point, three replicate filters were analyzed for each cell type. The mean ± S.D. is given for three separate experiments. Panel C, apical exposure of the cells to 5.68 mM [14C]glucose (specific activity 1 nmol/200,000 dpm). Cells were incubated for 3.5 and 24 h, and the basolateral medium was analyzed for [14C]. The mean ± S.D. is given for four replicate filters done in one experiment.
ditive manner, since the total amount of FABP (i.e. liver and intestinal) is not proportional to the amount of transport.

The nature of the basolaterally secreted $^{3}$H-lipids components was analyzed by thin-layer chromatography. Following 24 h of apical incubation with $^{3}$H-oleate, the predominate lipids isolated from the basolateral media were triglycerides and free fatty acids. Similar levels of free fatty acids were identified in the basolateral media from Ala$^{54}$ and Thr$^{54}$ cells. In contrast, triglyceride secretion differed, where Thr$^{54}$ cells secreted a 5–6-fold greater amount of triglyceride compared to Ala$^{54}$ cells (Fig. 5). Secretion of cholesterol esters, although representing a small percent of total lipid, also consistently differed between the Ala$^{54}$ and Thr$^{54}$ cells (1.4% and 6% of the total secreted lipids for Ala$^{54}$ and Thr$^{54}$, respectively).

The differences in fatty acid transport across Ala$^{54}$ and Thr$^{54}$ transfected Caco-2 cells provides the first direct evidence that IFABP participates in the intracellular transport of dietary long-chain fatty acids in vivo. The mechanism of movement of fatty acids into enterocytes remains speculative. Fatty acids may require a membrane transport protein or alternatively, may enter a cell by passive diffusion. Putative fatty acid transport proteins have been identified in liver, heart, skeletal muscle, and adipocytes (14–17). Hamilton et al. (18) have demonstrated that fatty acid movement into clonal pancreatic B-cells, as well as phospholipid bilayer vesicles, occurs predominantly via passive diffusion of the non-ionized form across the plasma membrane rather than via a membrane protein carrier. If long-chain fatty acids enter enterocytes via diffusion, then any mechanism that increases the shuttling of fatty acids away from the inner membrane surface would drive the diffusion gradient toward greater uptake. We did not observe a significant difference in the cell-associated fatty acids in Ala$^{54}$ and Thr$^{54}$ Caco-2 cells at 3.5 h (57–60% and 54–58% of total radiolabel added apically) or at 24 h (77–85% and 79–83% of total radiolabel added apically), but it remains undetermined whether these fatty acids have been intracellularly absorbed (uptake) or whether a large portion remain membrane-bound. Our data confirmed that Caco-2 cells retain approximately 90% of their lipids intracellularly at 24 h post-incubation (12), yet we still observed that increasing the concentration of fatty acid presented apically to the transfected Caco-2 cells resulted in a net increase in lipid secretion from Thr$^{54}$ compared to Ala$^{54}$ cells at 24 h (Table III). Since dietary fat is usually ingested as a bolus, and intestinal absorption rates are very high (approximately 96%) and remarkably constant among individuals (19),

\[
\begin{array}{ccc}
\text{4-day} & \text{14-day} & \\
\text{Ala}^{54} & \text{Thr}^{54} & \text{Non-transfected} \\
\text{IFABP (mg/mg)} & 0.2 & 0.2 & 0.2 & 0.2 & 0.2 & 0 \\
\text{LFABP (mg/mg)} & 0.001 & 0.001 & 0.4 & 0.7 & 0.5 & 1.5 \\
\text{Transport (dpm \times 10^3)} & 60 \pm 3 & 110 \pm 8 & 54 \pm 2 & 42 \pm 4 & 05 \pm 6 & 56 \pm 3
\end{array}
\]
a high concentration of long-chain fatty acids within an enterocyte would be predicted following a high fat meal. Therefore, the effect of the Ala<sup>54</sup>→Thr substitution on lipid transport and secretion may be greatest immediately following a high fat meal.

Previous studies have indicated a direct relationship between levels of insulin resistance and increased concentrations of circulating free fatty acids and triglycerides (20–27). Free fatty acids normally provide an alternative fuel source to glucose for energy during periods of fasting. Increased concentrations of plasma free fatty acids inhibit glucose uptake in a dose-dependent fashion (25) and cause insulin resistance in target tissues such as muscle, and possibly stimulate increased insulin release from pancreatic β-cells (26). Alternatively, increased concentrations of triglycerides, independent of circulating free fatty acids, can also affect glucose metabolism. Triglycerides alone account for at least 25% of the total decrease of forearm glucose uptake and glucose oxidation following Intralipid infusion (27). The effect of triglycerides on carbohydrate metabolism seems to follow the same intracellular pathway as free fatty acids, since triglyceride hydrolysis increases the intracellular pool of free fatty acids, thereby enhancing β-oxidation and decreasing glucose utilization (27).

If Thr<sup>54</sup> IFABP also increases fatty acid transport and triglyceride release in intact jejunum, then individuals who express the Thr<sup>54</sup> IFABP genotype would be predicted to: 1) release intestinally absorbed dietary fatty acids to the lymph at a faster rate than individuals with the Ala<sup>54</sup> genotype and 2) process more dietary long-chain fatty acids into chylomicron triglycerides than individuals who express the Ala<sup>54</sup> IFABP genotype. Either or both of these processes would result in decreased rates of insulin-mediated glucose uptake and increased rates of insulin release from pancreatic β-cells, consistent with the observed insulin resistance and hyperinsulinemia found in subjects with the Thr<sup>54</sup> IFABP genotype (4). Of particular relevance is a comparison of the insulin responses to oral glucose (75 g) versus a mixed meal (20% protein, 40% carbohydrate, 40% fat) in subjects with the Ala<sup>54</sup> and Thr<sup>54</sup> IFABP genotypes. Although insulin responses for both of these studies were significantly greater in subjects with the Thr<sup>54</sup> genotype, a much greater difference between the two IFABP genotypes was observed following the mixed meal, which contained dietary fats. This is consistent with the results presented in the Caco-2 model system. However, further studies are needed to determine whether a more rapid rate of release of dietary lipid to circulation, or differential esterification of absorbed fatty acids, or both mechanisms, are actually contributing factors to the insulin resistance and hyperinsulinemia observed in individuals with the Thr<sup>54</sup> IFABP genotype. Direct measurements of absorption levels and oxidation rates of ingested long-chain fatty acids are currently being analyzed in Pimas homozygous for the Ala<sup>54</sup>- or the Thr<sup>54</sup>-encoding IFABP alleles.

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TABLE III

| [Oleic acid] | Ala<sup>54</sup> | Thr<sup>54</sup> | Thr<sup>54</sup>[Ala<sup>54</sup>] |
|-------------|----------------|----------------|-------------------------------|
| 100         | 130 ± 11       | 247 ± 15       | 1.9                           |
| 150         | 305 ± 14       | 631 ± 31       | 2.0                           |
| 200         | 1,635 ± 50     | 3,695 ± 71     | 2.3                           |
| 250         | 2,394 ± 289    | 6,582 ± 220    | 2.8                           |
| 300         | 7,826 ± 881    | 21,150 ± 1280  | 2.7                           |

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