Transcytosis of Albumin in Astrocytes Activates the Sterol Regulatory Element-binding Protein-1, Which Promotes the Synthesis of the Neurotrophic Factor Oleic Acid*

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Arantxa Tabernero‡§, Ana Velasco§, Begoña Granda, Eva M. Lavado, and José M. Medina**
From the Departamento de Bioquímica y Biología Molecular, Facultad de Farmacia, Universidad de Salamanca, 37007 Salamanca, Spain and the ¶Unidad de Investigación, Hospital Universitario de Salamanca, 37007 Salamanca, Spain

We have recently reported that albumin, a serum protein present in the developing brain, stimulates the synthesis of oleic acid by astrocytes, which promotes neuronal differentiation. In this work, we gain insight into the mechanism by which albumin induces the synthesis of this neurotrophic factor. Our results show that astrocytes internalize albumin in vesicle-like structures by receptor-mediated endocytosis. Albumin uptake was followed by transcytosis, including passage through the endoplasmic reticulum, which was required to induce the synthesis of oleic acid. Oleic acid synthesis is feedback-regulated by the sterol regulatory element-binding protein-1, which induces the transcription of stearoyl-CoA 9-desaturase, the key rate-limiting enzyme for oleic acid synthesis. In our research, the presence of albumin activated the sterol regulatory element-binding protein-1 and increased stearoyl-CoA 9-desaturase mRNA. Moreover, when the activity of sterol regulatory element-binding protein-1 was inhibited by overexpression of a truncated form of this protein, albumin did not affect stearoyl-CoA 9-desaturase mRNA, indicating that the effect of albumin is mediated by this transcription factor. The effect of albumin was abolished when traffic to the endoplasmic reticulum was prevented or when albumin was accompanied with oleic acid. In conclusion, our results suggest that the transcytosis of albumin includes passage through the endoplasmic reticulum, where oleic acid is sequestered, initiating the signal cascade leading to an increase in its own synthesis.

Astrocytes, the main glial cell population in the central nervous system, play a major role in supporting the development of neurons. In fact, astrocytes synthesize and release extracellular matrix proteins and adhesion molecules, which participate not only in the migration of neurons but also in the formation of neuronal aggregates. In addition, astrocytes produce a broad spectrum of growth factors and cytokines, which can regulate the morphology, proliferation, differentiation, and survival of neurons (for a review, see Ref. 1). We (2) have recently shown that astrocytes synthesize oleic acid from the main metabolic substrates, and oleic acid is released to the extracellular medium. Oleic acid is then incorporated in neurons, specifically into growth cones, and its presence promotes neuronal differentiation. Thus, the presence of oleic acid induces axonal growth, neuronal clustering, and expression of the axonal growth-associated protein-43 (GAP-43) by a protein kinase C-dependent mechanism. All these observations indicate that oleic acid behaves as a neurotrophic factor. The signal that triggers oleic acid synthesis in astrocytes is the serum protein albumin (2). It is well documented that albumin reaches high concentrations in the brain and the cerebrospinal fluid of newborn mammals, unlike the situation in adults (3–5). The presence of albumin in the brain may be due to the existence of a mechanism through which albumin is transferred from the blood to the brain and cerebrospinal fluid that is active only in the immature brain (6, 7). In addition, the in situ synthesis of albumin can also contribute to the increased albumin levels found in the newborn brain (8).

It is also well known that oleic acid synthesis is regulated by the sterol regulatory element-binding protein-1 (SREBP-1), a basic-helix-loop-helix-leucine zipper transcription factor that induces enzymes involved in oleic acid synthesis such as acetyl-CoA carboxylase, ATP citrate (pro-S)-lyase, fatty acid synthase, NADPH-producing enzymes, and stearoyl-CoA 9-desaturase (SCD) (9–12). Like other members of the SREBP family, SREBP-1 is located in the endoplasmic reticulum (ER) and is activated by proteolysis, releasing an active mature form that binds to the promoters of genes containing sterol-responsive elements (SRE, for a review, see Ref. 13). A critical committed step in the synthesis of oleic acid is the introduction of the cis-double bond in the Δ9 position, catalyzed by SCD, an enzyme also located in the ER that is transcriptionally activated by SREBP-1 because its gene contains the SRE (14). Oleic acid synthesis is feedback-regulated because oleic acid suppresses SREBP-1 activation (15–17) and SCD induction (18), both of which accompany the decrease in oleic acid synthesis (19).

Because the presence of albumin in the brain is developmentally regulated, it has been suggested that this protein could play an important role in neural cell differentiation (4). In agreement with this, albumin induces the synthesis and re-
leak of oleic acid by astrocytes, which behaves as a neurotrophic factor (2). However, the mechanism by which albumin induces oleic acid synthesis and release by astrocytes is far from clear. Therefore, in this work we investigated the mechanism by which albumin promotes oleic acid synthesis in astrocytes.

**EXPERIMENTAL PROCEDURES**

**Animals**—Albino Wistar rats, fed ad libitum on a stock laboratory diet (49.8% carbohydrates, 23.5% protein, 3.7% fat, 5.5% (w/v) minerals, and added vitamins and amino acids), were used for the experiments. Rats were kept on a 12-h light-dark cycle. Postnatal day 1 newborn rats were used to prepare astrocytes.

**Astrocyte Culture**—Astrocyte cultures were prepared and cultured in DMEM + 10% fetal calf serum as reported previously (20). Briefly, animals were decapitated, and their brains were immediately excised. After removing the meninges and blood vessels, cells were dissociated from the forebrains. Cells were plated onto poly-l-lysine (10 μg/ml)-coated Petri dishes at a density of 1.0 × 10^6 cells/cm².

**Albumin Loading and Unloading from Astrocytes**—14 DIV astrocytes were loaded at 37 °C in Elliot buffer (21) (11 mM sodium phosphate, 122 mM NaCl, 4.8 mM KCl, 0.4 mM KH₂PO₄, 1.2 mM MgSO₄, and 1.3 mM CaCl₂, pH 7.4) containing 5 mM glucose and 2% (w/v) bovine serum albumin conjugated to fluorescein isothiocyanate (FITC-BSA; Sigma) as described (23). After 10 min of loading at 37 °C in Elliot buffer plus 2% (w/v) BSA. For the unloading experiments, loaded astrocytes were kept in Elliot buffer plus 2% (w/v) BSA at 37 °C or 4 °C. At different times, the cells were visualized by confocal microscopy (excitation at 488 nm; Zeiss LSM 510), and the medium was recovered as described.

At different times, the cells were visualized by confocal microscopy (excitation at 488 nm; Zeiss LSM 510), and the medium was recovered as described (20). Briefly, animals were decapitated, and their brains were immediately excised. After removing the meninges and blood vessels, cells were dissociated from the forebrains. Cells were plated onto poly-l-lysine (10 μg/ml)-coated Petri dishes at a density of 1.0 × 10^6 cells/cm².

For the experiments with the inhibitors, 14 DIV astrocytes were preincubated at 37 °C in PBS containing 2 mM EDTA and 0.25% trypsin or 0.1% Pronase from Streptomyces griseus type XIV (Sigma) for 5 min. For treatment with lectins, 14 DIV astrocytes were preincubated at 37 °C in PBS containing 2 mM EDTA and 0.25% trypsin or 0.1% Pronase from Streptomyces griseus type XIV (Sigma) for 5 min. Controls were carried out by preincubating cells in PBS with 2 mM EDTA. Because protease digestion disrupts the cell monolayer, astrocytes were collected, washed, and allowed to attach to the Petri dish for 1 h before loading with FITC-BSA. Apart from protamine, trypsin, or Pronase, the inhibitors were maintained at the same concentration for the rest of the experiments.

**Cell Incubation**—Cell incubations were carried out as described previously (20). 14 DIV astrocytes grown on Petri dishes (25 cm²) were incubated at 37 °C for 1 h with 1.5 ml of Elliot buffer containing cold and radiolabeled substrates in the absence or presence of BSA as indicated. For the experiments with the inhibitors, 14 DIV astrocytes were preincubated at 37 °C with 1 μM PAO, 30 μM monensin, 30 μM nocardazole, 100 μM colchicine, or 40 μM brefeldin A (BFA) for 20 min. For treatment with lectins or proteases, 14 DIV astrocytes were preincubated at 37 °C in PBS containing 2 mM EDTA and 0.25% trypsin or 0.1% Pronase from Streptomyces griseus type XIV (Sigma) for 5 min. Controls were carried out by preincubating cells in PBS with 2 mM EDTA. Because protease digestion disrupts the cell monolayer, astrocytes were collected, washed, and allowed to attach to the Petri dish for 1 h before loading with FITC-BSA. Apart from protamine, trypsin, or Pronase, the inhibitors were maintained at the same concentration for the rest of the experiments.

**Analysis of Oleic Acid by HPLC**—Oleic acid synthesized and released by astrocytes is far from clear. Therefore, in this work we investigated the mechanism by which albumin promotes oleic acid synthesis in astrocytes.

**Electrophoretic Analysis of the Astrocyte Incubation Medium**—The medium recovered after the incubation was subjected to native gel electrophoresis in 10% polyacrylamide gel, pH 8.9, following the manufacturer’s instructions (Clean Gel, Amersham Biosciences, Inc.). When the migration had finished, the gel was cut into three portions. One portion was incubated with 0.1% (w/v) Coomassie Blue. A second gel portion was incubated with 3% (w/v) cupric acetate in 8% (v/v) orthophosphoric acid and dried at 110 °C. The third gel portion was exposed for 30 days to an autoradiography film at −70 °C.
microscopy (Fig. 1, A and C) and quantified from digitized fluorescence photomicrographs (Fig. 1E). As can be seen in Fig. 1A, astrocytes were conspicuously loaded with FITC-BSA in discrete vesicle-like structures. Under these circumstances, PAO inhibited albumin internalization because only a few fluorescence spots were observed in the phase-contrast fluorescence superimposed photomicrographs (Fig. 1C). In fact, PAO inhibited FITC-BSA uptake by about 75% (Fig. 1E). To confirm the participation of an albumin-binding protein in albumin endocytosis, cells were treated with trypsin or Pronase, proteases that inhibit endocytosis by receptor proteolysis, or with L. flavus agglutinin or G. max agglutinin, lectins that block glycoprotein-mediated endocytosis by binding to glycosyl residues (29). It should be mentioned that L. flavus agglutinin binds to N-acetylneuraminyl or N-glycolylneuraminyl residues, whereas G. max agglutinin binds to N-acetylgalactosaminyl or galactosaminyl residues. Our results showed that after 5 min of treatment with trypsin or Pronase, astrocytes lost their ability
to take up albumin (Fig. 1E). In addition, G. max agglutinin (but not L. flavus agglutinin) inhibited albumin internalization by about 70%. Furthermore, the presence of the specific hapten of G. max agglutinin, GalNAc, prevented the G. max agglutinin effect. Finally, protamine, a basic protein that inhibits absorptive-mediated endocytosis (30), was also tested, but its presence did not modify albumin uptake (Fig. 1E).

When FITC-BSA-loaded astrocytes were allowed to unload, very little fluorescence remained inside the cell after 1 h (Fig. 1B). In order to know the kinetics of BSA release, loaded astrocytes were exposed to 2% (w/v) BSA and medium, and cell fluorescence was followed over 90 min at 37 °C (Fig. 1G). The decrease in cell fluorescence was seen to be concurrent with an increase in the fluorescence of the medium, suggesting that FITC-BSA was gradually released from astrocytes. The fluorescence of the medium and of the cells showed a linear and inverse correlation (R² = 0.886; p < 0.001). FITC-BSA release was abolished at 4 °C (Fig. 1G), suggesting that the observed FITC-BSA release was an active process (see also Ref. 31). Furthermore, our results revealed that inhibitors of transcytosis, such as BFA (Fig. 1D), monensin, nocodazole, or colchicine (32), inhibited FITC-BSA release. Unloading was reduced to about 80% by the presence of monensin and to about 50–60% by the presence of BFA, nocodazole, or colchicine, as judged by the amount of fluorescence remaining inside the cells and the fluorescence recovered from the incubation medium (Fig. 1F).

It should be noted that albumin uptake was not modified by the presence of brefeldin A, monensin, nucodazole, or colchicine (data not shown).

Astrocytes Release Oleic Acid Along with Albumin—Our results show that inhibitors of albumin endocytosis, such as PAO, inhibit oleic acid synthesis and release by astrocytes by about 90% (Fig. 2A). Likewise, oleic acid synthesis and release was also inhibited by several inhibitors of transcytosis, such as monensin (94%), nocodazole (46%), or BFA (43%) (Fig. 2A). In addition, our observations suggest that oleic acid leaves astrocytes as a fatty acid-albumin complex. Thus, polyacrylamide gel electrophoretic analysis of the medium after incubation of astrocytes for 1 h with 10 mM lactate + 100–150 dpm/nmol [14C]lactate in the presence of 2% (w/v) BSA revealed that the putative fatty acid-BSA complex had the same Rf, regardless of whether the gel was developed for proteins, fatty acids, or radioactivity (Fig. 2B). These results clearly indicate that the radiolabeled oleic acid was bound to albumin in the medium recovered after the incubation. However, the possibility that the oleic acid-albumin complex could be formed in the extracellular medium after the release of free oleic acid from the cells cannot be excluded because albumin was always present in the extracellular medium throughout the experiment. To confirm that the oleic acid-BSA complex is indeed formed inside the cell and then released to the extracellular medium, astrocytes were loaded with FITC-BSA in the presence of radiolabeled substrates. After washing, FITC-BSA was allowed to unload from astrocytes, and the presence of oleic acid complexed to FITC-BSA was analyzed. Our results revealed that in electrophoresis, the FITC-BSA released from astrocytes migrates together with radiolabeled oleic acid (Fig. 2C). In addition, monensin, which inhibits albumin exocytosis, dramatically reduced the amount of FITC-BSA and radiolabeled oleic acid released from astrocytes to the extracellular medium (Fig. 2C). These results suggest that the complex is formed inside the cell before being released to the extracellular medium.

Albumin Induces Stearoyl-CoA 9-desaturase through the Activation of the Sterol Regulatory Element-binding Protein—To gain insight into the mechanism by which albumin enhances oleic acid synthesis, we investigated the possible changes in mature/precursor forms of SREBP-1, a transcription factor that stimulates oleic acid synthesis (11, 12). Oleic acid protects SREBP-1 proteolysis by preventing the cleavage and release of low molecular mass SREBP-1 mature form (15–17), which induces the enzymes involved in oleic acid synthesis (11, 12, 18). In this context, our results show that albumin increases the amount of the low molecular mass SREBP-1 mature form, whereas it decreases that of the high molecular mass SREBP-1 inactive precursor (Fig. 3A). The effect of albumin on SREBP-1 proteolysis was avoided by the presence of 100 μM oleic acid or 50 μM nucodazole (the latter inhibits the transport of proteins to the ER (33)) (Fig. 3A).
To confirm whether SREBP-1a is directly involved in the stimulation of oleic acid synthesis caused by albumin, we used a truncated form of the SREBP protein that binds to the SRE-1 site of the SCD gene, preventing the stimulation of SCD transcription caused by SREBP-1a. The truncated form of SREBP-1a containing amino acids 92–410 has been reported to be an efficient inhibitor of the transcriptional activity of SREBP-1a. In fact, this truncated protein retains the ability to translocate to the nucleus and bind to SRE-1, preventing the binding of SREBP-1a (34). Accordingly, we designed experiments to overexpress this truncated form of SREBP-1a in astrocytes and to test the effect of albumin under these circumstances. A construction designated pGFSREBP was made that results in the expression of the truncated SREBP-1 protein (92–410) as a fusion to the C terminus of the GFP. Astrocytes were then transfected with pEGFP or with pGFSREBP. After 24 h, the cells were incubated with albumin for 8 h, and the level of expression of the SCD mRNA was analyzed by fluorescence in situ hybridization (Fig. 3, C–F). Astrocytes transfected with pGFSREBP (Fig. 3, C and E) showed a clear translocation of the truncated protein to the nucleus (Fig. 3C, arrows). In addition, SCD mRNA was not increased in pGFSREBP-transfected astrocytes (Fig. 3E; note the absence of SCD mRNA in the transfected astrocyte, indicated by arrows), whereas it was strongly enhanced in non-transfected astrocytes (other cells in Fig. 3E) by the presence of albumin. The overexpression of GFP (Fig. 3D) did not modify the effect of albumin on SCD mRNA expression (Fig. 3F).

**DISCUSSION**

We (2) have recently shown that astrocytes synthesize and release oleic acid, which induces neuronal differentiation. The signal that triggers oleic acid synthesis and release by astrocytes is albumin (2), a serum protein that is specifically taken up by the brain during development (3, 4, 6, 7). In this work, we show that astrocytes take up albumin by receptor-mediated endocytosis and that this is followed by translocation (see also Ref. 31) and exocytosis (Fig. 1). Thus, the existence of absorptive-mediated endocytosis can be precluded because albumin uptake was not affected by the presence of protamine (Fig. 1F), an inhibitor of this process (30). On the other hand, albumin internalization was inhibited by PAO (Fig. 1E), an inhibitor of receptor-mediated endocytosis (28). Our results are consistent with the idea that an albumin-binding protein located on the astrocytic plasma membrane would be involved in albumin uptake. In consonance with this, a brief treatment with proteases prevented albumin internalization in astrocytes (Fig. 1E), suggesting that albumin internalization is mediated by a protein that acts as a putative albumin receptor. This would probably be a glycoprotein containing N-acetylglalactosaminyl or galactosaminy1 residues because albumin endocytosis was inhibited by *G. max* agglutinin (Fig. 1E), a lectin that binds to these glycoprotein residues (29). Our results also suggest that, once inside the astrocyte, albumin moves by vesicle-mediated transcytosis (Fig. 1A). In fact, FITC-BSA release was a temperature-dependent process (Fig. 1G) and was inhibited by micotubule-disrupting agents such as nucodazole or colchicine (Fig. 1F), suggesting that albumin is transported by micotubule-guided vesicles from the Golgi to the ER (30). Moreover, albumin release by astrocytes was inhibited by BFA and monensin (Fig. 1D and F), both of which prevent vesicular trafficking from the ER to the Golgi (35) or from this to the plasma membrane (36), respectively.

Our results show that the inhibition of endocytosis, transcytosis, or exocytosis by protein trafficking inhibitors is associated with a significant inhibition of oleic acid synthesis and/or release by astrocytes (Fig. 2A). Therefore, it may be concluded that the passage of albumin through the astrocyte promotes oleic acid synthesis. Moreover, both BFA and nucodazole inhib-
the intracellular trafficking of FITC-BSA (Fig. 1), indicating that albumin would pass through the ER (33). Because albumin shows a high affinity for oleic acid (37) and because this fatty acid is synthesized in the ER, it is reasonable to suggest that albumin sequestrates oleic acid in the ER (33). Because the transfer of albumin from the blood to the brain across the blood-brain barrier is developmentally regulated (6), it is easy to speculate that during development, the end feet of astrocytes take up albumin, which is then translocated to the ER, inducing oleic acid synthesis. The oleic acid-albumin complex would then be released to the extracellular medium in contact with neurons to promote its differentiation (Fig. 4).

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