Dystroglycan Is a Dual Receptor for Agrin and Laminin-2 in Schwann Cell Membrane*

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We have shown previously that α-dystroglycan with a molecular mass of 120 kDa is a Schwann cell receptor of laminin-2, the endoneurial isoform of laminin comprised of the α2, β1, and γ1 chains. In this paper, we show that Schwann cell α-dystroglycan is also a receptor of agrin, an acetylcholine receptor-aggregating molecule having partial homology to laminin chains in the C terminus. Immunochemical analysis demonstrates that the peripheral nerve isoform of agrin is a 400-kDa component of the endoneurial basal lamina and is co-localized with α-dystroglycan surrounding the outermost layer of myelin sheath of peripheral nerve fibers. Blot overlay analysis demonstrates that both endoneurial peripheral nerve agrin and laminin-2 bind to Schwann cell α-dystroglycan. Recombinant C-terminal fragment of the peripheral nerve isoform of agrin also binds to Schwann cell α-dystroglycan, confirming that the binding site for Schwann cell α-dystroglycan resides in the C terminus of agrin molecule. Furthermore, the binding of recombinant agrin C-terminal fragment to Schwann cell α-dystroglycan competes with that of laminin-2. All together, these results indicate that α-dystroglycan is a dual receptor for agrin and laminin-2 in the Schwann cell membrane.

Dystroglycan is encoded by a single gene and cleaved into two proteins, α- and β-dystroglycan, by post-translational processing (1). Skeletal muscle α-dystroglycan with a molecular mass of 156 kDa is a laminin-binding extracellular peripheral membrane glycoprotein anchored to the sarcolemma by a transmembrane glycoprotein β-dystroglycan (1, 2). On the cytoplasmic side of the sarcolemma, β-dystroglycan binds to a cytoskeletal protein dystrophin (3, 4) and is presumed to play a role in signal transduction (5).

Laminin is a heterotrimer made up of three chains of classes α, β, and γ and exists in numerous trimeric isoforms in different tissues (for a review see Ref. 6). Laminin α chains have globular domain (G) repeats in the C terminus, and laminin-1, comprised of the α1, β1, and γ1 chains, binds to α-dystroglycan via the last two G repeats in the α1 chain (7). In peripheral nerve, laminin-2, comprised of the α2, β1, and γ1 chains, is expressed in the endoneurial basal lamina (8, 9), and we have shown recently that α-dystroglycan with a molecular mass of 120 kDa is a Schwann cell receptor of laminin-2 (10, 11). Because peripheral myelination is disturbed in congenital muscular dystrophy patients and dy mice deficient in laminin α2 chain (12–18), these findings suggest a role for the interaction of α-dystroglycan with laminin-2 in peripheral myelogenesis. Recently, skeletal muscle α-dystroglycan was shown to bind agrin, which has the G repeats homologous to those of laminin α chains in the C terminus and mediates the clustering of acetylcholine receptors (AChRs) in the neuromuscular junction (19–23). Agrin has several isoforms generated by alternative mRNA splicing at two sites in the C terminus (named A and B in chick and Y and Z in rat) (23–26). Agrin isoforms are expressed among many different tissues, but the neuronal isoform, which has inserts of four and eight amino acids at the A and B sites, respectively, has the highest activity of AChR clustering (23–26). On the other hand, the biological functions of non-neuronal isoforms having no inserts in the A and B sites are unknown. Previously, immunoreactivity for agrin was demonstrated in peripheral nerve by immunohistochemistry; however, it was unclear if the observed immunoreactivity was with authentic agrin or other immunologically-related molecules (27). Furthermore, elucidation of the biological functions of putative peripheral nerve agrin requires identification of its receptor. To address these issues, we have characterized agrin and its receptor in peripheral nerve.

EXPERIMENTAL PROCEDURES

Immunochemical Analysis—Affinity-purified sheep antibody against dystroglycan fusion protein D, monoclonal antibody 43DA2/8D5 against the C terminus of β-dystroglycan, monoclonal antibody 2D9 against the proximal portion of the G domain of human laminin α2 chain, and rabbit antisera against recombinant chick agrin were described previously (1, 26, 28–30). Affinity-purified rabbit antibody

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† The abbreviations used are: G, globular; AChR, acetylcholine receptor; BSA, bovine serum albumin; HSPG, heparan sulfate proteoglycan; WGA, wheat germ agglutinin; EHS, Engelbreth-Holm-Swarm; PAGE, polyacrylamide gel electrophoresis.
against mouse EHS sarcoma laminin and monoclonal antibody HepSS-1 against heparan sulfate glycosaminoglycan were purchased from Sigma and Seikagaku Corporation, respectively. 3–12% SDS-PAGE, immunoblotting, and immunohistochemical analysis of bovine peripheral nerve were performed as described previously (10, 11). Double immunostaining analysis of bovine peripheral nerve was performed using either a mixture of monoclonal antibody 43DA/SDS and rabbit antiseraum against recombinant chick agrin or a mixture of monoclonal antibody 43DA/SDS and affinity-purified rabbit antibody against mouse EHS sarcoma laminin. Immunoreaction was detected using rhodamine-conjugated goat anti-mouse IgG antibody (Boehringer Mannheim) and biotinylated goat anti-rabbit IgG antibody (Vector) followed by fluorescein isothiocyanate-conjugated streptavidin (Jackson ImmunoResearch).

**Alkaline Extraction of Crude Peripheral Nerve Membranes—Crude bovine peripheral nerve membranes were suspended at a protein concentration of 2.5 mg/ml in 50 mM Tris-HCl, pH 7.4, containing a mixture of protease inhibitors: benzamidine (0.75 mM), phenylmethylsulfonyl fluoride (0.1 mM), pepstatin A (0.7 μM), aprotinin (78 μM), and leupeptin (1.1 μM). The suspension was titrated to pH 11, extracted for 1 h at room temperature, and centrifuged at 140,000 × g for 30 min at 25°C. Supernatants were collected by decanting and titrated to pH 7.4. The pellets were suspended in the original volume of buffer A containing 0.5 mM NaCl. The suspension was titrated to pH 12 and extracted for 1 h at room temperature. The suspension was titrated to pH 11 and centrifuged at 140,000 × g for 30 min at 25°C. The supernatants were collected by decanting, and titrated to pH 7.4, and cooled to 4°C on ice. After being titrated to pH 7.4 again, the supernatants were centrifuged at 140,000 × g for 30 min at 4°C. The supernatants were circulated over 50 ml of wheat germ agglutinin (WGA)-Sepharose (Pharmacia Biotech Inc.) at 4°C overnight. The WGA-Sepharose was washed with buffer A containing 0.5 mM NaCl and then eluted with buffer A containing 0.3 M GlcNAc. 10 mI of laminin-Sepharose (2.5 mg/ml) (11) was blocked with buffer A containing 1 mM CaCl₂, 1 mM MgCl₂, and 3% bovine serum albumin (BSA) at 4°C for 2 h and then washed with buffer A containing 1 mM CaCl₂ and 1 mM MgCl₂. The pooled GlcNAc eluates of WGA-Sepharose were circulated over laminin-Sepharose at 4°C overnight in the presence of 1 mM CaCl₂ and 1 mM MgCl₂. After washing with buffer A containing 1 mM CaCl₂ and 1 mM MgCl₂, the laminin-Sepharose was eluted with buffer A containing 10 mM EDTA.

**Identification and Isolation of Peripheral Nerve Proteins That Bind to Schwann Cell α-Dystroglycan—Crude bovine peripheral nerve membranes (250 mg) were suspended in buffer A at a protein concentration of 10 mg/ml. The suspension was titrated to pH 12, extracted for 1 h at room temperature, and centrifuged at 140,000 × g for 30 min at 25°C. The supernatants were collected by decanting and titrated to pH 7.4 (pH 12 extracts). Nitrocellulose transfers of isolated Schwann cell α-dystroglycan were blocked in 10 mM triethanolamine, pH 7.6, 140 mM NaCl, 1 mM CaCl₂, and 1 mM MgCl₂ (LLBB) containing 5% nonfat dry milk (MLLB) for 1 h at room temperature, and then incubated with the pH 12 extracts of the crude bovine peripheral nerve membranes in the presence of 1 mM CaCl₂ and 1 mM MgCl₂ overnight at 4°C. After washing twice for 10 min at room temperature in MLBB, nitrocellulose transfers were incubated with rabbit antisera against recombinant chick agrin or affinity-purified rabbit antibody against mouse EHS sarcoma laminin in MLBB overnight at room temperature. After washing twice for 10 min at room temperature in MLBB, nitrocellulose transfers were incubated with peroxidase-labeled goat anti-rabbit IgG (Boehringer Mannheim) in MLBB for 2 h at room temperature, washed twice for 10 min at room temperature in MLBB, and then developed using 4-chloro-1-naphthol as substrate.

**Isolated Schwann cell α-dystroglycan (0.2 mg) was concentrated using a Centricron 30 (Amicon), separated by 3–12% SDS-PAGE, and transferred to a nitrocellulose membrane. The nitrocellulose transfer in the range of 100–140 kDa of molecular weight was excised (α-dystroglycan strip). After blocking in LLLB containing 3% BSA (BSA-LLBB) for 2 h at room temperature, the α-dystroglycan strip was incubated with 60 ml of the pH 12 extracts of the crude bovine peripheral nerve membranes in the presence of 1 mM CaCl₂ and 1 mM MgCl₂ overnight at 4°C. After washing five times for 10 min at room temperature in LBB, the α-dystroglycan strip was eluted with 3 ml of LBB containing 20 mM EDTA. Blot overlay of isolated Schwann cell α-dystroglycan with recombinant agrin C-terminal fragment or laminin-2—Recombinant agrin c95A0B0, which corresponds to the C-terminal 95-kDa fragment of chick agrin and lacks inserts at both A and B sites, was prepared as described previously (26, 30). Laminin-2 was isolated from human placenta as described previously (26, 30). The C-terminal 95-kDa fragment of chick agrin and/or human placenta laminin-2 was performed as described above, except that instead of the pH 12 extracts of the crude bovine peripheral nerve membranes, nitrocellulose transfers were incubated with c95A0B0 and/or human placenta laminin-2 in BSA-LLBB overnight at room temperature.

**RESULTS AND DISCUSSION**

Membrane-associated cytoskeletal and peripheral membrane proteins are extracted from the membranes at pH 11 and 12, respectively, whereas integral membrane proteins are not extracted under these conditions (31). Based on this, we performed alkaline extraction of the crude bovine peripheral nerve membranes. The extracellular matrix protein laminin α2 chain of 320 kDa was only partially extracted at pH 11 but almost completely extracted at pH 12 (Fig. 1). Laminin β1 and γ1 chains were also only partially extracted at pH 11 but almost completely extracted at pH 12 (not shown). The molecular mass of native agrin has been obscure for a long time, although the primary structure has indicated that the core protein is about 220 kDa in size (32, 33). Very recently, chick brain agrin and recombinant chick agrin expressed in transfected COS cells...
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were both identified as diffuse smears of over 400 kDa on SDS gel (26, 34). In the crude bovine peripheral nerve membranes, agrin was identified as a diffuse smear of 400 kDa, which was only partially extracted at pH 11 but almost completely extracted at pH 12 (Fig. 1). Thus, the behavior upon alkaline extraction was similar for agrin and laminin-2. Similar to the laminin α2 chain, furthermore, a substantial amount of agrin was extracted from the crude bovine peripheral nerve membranes by 10 mM EDTA (not shown). These results suggest that like laminin-2, agrin may also be a component of the extracellular matrix in the peripheral nerve. Recently, chick brain agrin was shown to be a heparan sulfate proteoglycan (HSPG) (34). In the crude bovine peripheral nerve membranes, antibody against HSPG identified several proteins but did not react with the 400-kDa agrin smear (Fig. 1), suggesting that agrin is not a major HSPG in bovine peripheral nerve or alternatively that the epitope recognized by the antibody is not contained in bovine peripheral nerve agrin.

The results of immunohistochemical analysis of bovine peripheral nerve are shown in Fig. 2. Agrin was localized surrounding the outermost layer of myelin sheath of peripheral nerve fibers, together with α- and β-dystroglycan and laminin α2 chain (Fig. 2). Double immunostaining, 1) for dystroglycan and laminin and 2) for dystroglycan and agrin, confirmed the co-localization of dystroglycan, laminin, and agrin surrounding the outermost layer of the myelin sheath of peripheral nerve fibers (Fig. 3). Together with the extraction data described above and the reported primary structure (30, 32, 33), these results indicate that like laminin-2, agrin is a component of the endoneurial basal lamina surrounding the myelin sheath of peripheral nerve fibers. Laminin and agrin were also detected in the basal lamina surrounding capillaries, but dystroglycan was not detected in the capillaries (Fig. 3).

The results so far raise a possibility that α-dystroglycan may be an agrin receptor in the Schwann cell membrane. α-Dystroglycan, which is an extracellular peripheral membrane protein, is known to be extracted from the membranes at pH 12 (31). In addition, Schwann cell α-dystroglycan binds to WGA and laminin-Sepharose specifically (11). Based on these findings, we isolated, using WGA and laminin affinity chromatographies, Schwann cell α-dystroglycan from the pH 12 extracts of the crude bovine peripheral nerve membranes and asked if it would bind agrin in vitro.

First we tested the binding of peripheral nerve agrin to Schwann cell α-dystroglycan. As described above, both peripheral nerve agrin and laminin are completely extracted from the crude bovine peripheral nerve membranes at pH 12 (Fig. 1). So, we overlaid, in the presence of 1 mM CaCl₂ and 1 mM MgCl₂, the nitrocellulose transfers of isolated Schwann cell α-dystroglycan with the pH 12 extracts of the crude bovine peripheral nerve membranes and detected the peripheral nerve agrin and laminin which bound to α-dystroglycan with specific antibodies. As shown in Fig. 4A, both endogenous peripheral nerve agrin and laminin bound to the 120-kDa Schwann cell α-dystroglycan. In order to isolate the peripheral nerve proteins that bind to Schwann cell α-dystroglycan, the nitrocellulose transfer strip of Schwann cell α-dystroglycan was incubated in the presence of 1 mM CaCl₂ and 1 mM MgCl₂ with the pH 12 extracts of the crude bovine peripheral nerve membranes, washed extensively, and then eluted with a buffer containing 20 mM EDTA. Immunoblot analysis of the eluates demonstrated that both endogenous peripheral nerve agrin of 400 kDa and laminin α2
The agrin C-terminal domain contains amino acid sequences homologous to the G repeats of laminin α chains involved in the binding to α-dystroglycan (7). In addition, previous results have suggested that putative peripheral nerve agrin lacks inserts at both A and B sites in the C terminus (24). Based on chain of 320 kDa were isolated by these procedures (Fig. 4B).

Fig. 4. A, identification of peripheral nerve proteins that bind to Schwann cell α-dystroglycan. Isolated bovine Schwann cell α-dystroglycan (3 µg) was separated by 3–12% SDS-PAGE, transferred to nitrocellulose membranes, and then overlaid with the pH 12 extracts of the crude bovine peripheral nerve membranes. Laminin and agrin that bound to α-dystroglycan were detected with affinity-purified rabbit antibody against mouse EHS sarcoma laminin (Anti-Laminin) and rabbit antiserum 707 against recombinant chick agrin (Anti-Agrin), respectively. + and − indicate the nitrocellulose transfers overlaid or not overlaid with the pH 12 extracts, respectively. CB indicates the SDS gel stained with Coomassie Blue. Molecular mass standards (Da × 10^2) are shown on the left. B, isolation of peripheral nerve proteins that bind to Schwann cell α-dystroglycan. Isolated bovine Schwann cell α-dystroglycan (0.2 mg) were separated by 3–12% SDS-PAGE and transferred to a nitrocellulose membrane. The nitrocellulose transfer in the range of 100–140 kDa of molecular weight was excised and incubated with the pH 12 extracts of isolated bovine peripheral nerve membranes. The proteins that bound to the strip was eluted with a buffer containing 20 mM EDTA and analyzed by immunoblotting with 2D9 (Anti-Lam a2) or rabbit antiserum 707 against recombinant chick agrin (Anti-Agrin). Molecular mass standards (Da × 10^2) are shown on the left.

Fig. 5. A, the binding of recombinant chick agrin C-terminal fragment c95A0B0 to Schwann cell α-dystroglycan. Nitrocellulose transfers of isolated bovine Schwann cell α-dystroglycan (1 µg) were overlaid with 5 nM c95A0B0 in BSA-LBB (Control), in BSA-LBB containing 10 mM EDTA (+ EDTA), in BSA-LBB containing 10 mM EDTA and 20 mM CaCl2 (+ EDTA & Ca), in BSA-LBB containing 10 mM EDTA and 20 mM MgCl2 (+ EDTA & Mg), or in BSA-LBB containing 0.5 M NaCl (+ NaCl). c95A0B0 that bound to α-dystroglycan was detected using rabbit antiserum 707 against recombinant chick agrin. Molecular mass standards (Da × 10^2) are shown on the left. B, the binding of recombinant chick agrin C-terminal fragment c95A0B0 (Agrin) and human placenta laminin-2 (Laminin-2) to Schwann cell α-dystroglycan. Nitrocellulose transfers of isolated bovine Schwann cell α-dystroglycan (3 µg) were overlaid with 5 nM laminin-2 (first lane), 5 nM laminin-2 and 50 nM c95A0B0 (second lane), 5 nM c95A0B0 (third lane), or 5 nM c95A0B0 and 50 nM laminin-2 (fourth lane). Laminin-2 and c95A0B0 that bound to α-dystroglycan were detected with affinity-purified rabbit antibody against mouse EHS sarcoma laminin (first and second lanes) and rabbit antiserum 707 against recombinant chick agrin (third and fourth lanes), respectively. Molecular mass standards (Da × 10^2) are shown on the left.
these findings, we tested the binding of recombinant agrin C-terminal fragment c95\textsubscript{A0B0}, lacking inserts at both the A and B sites, to Schwann cell α-dystroglycan. Blot overlay analysis demonstrated that in the presence of 1 mM CaCl\textsubscript{2} and 1 mM MgCl\textsubscript{2}, c95\textsubscript{A0B0} bound to the 120-kDa Schwann cell α-dystroglycan (Fig. 5A), indicating that 1) the binding site for Schwann cell α-dystroglycan resides in the C terminus of agrin molecule and 2) amino acid inserts at the A and B sites are not required for this binding. The binding of c95\textsubscript{A0B0} was significantly reduced by the inclusion of 10 mM EDTA in the overlay medium (Fig. 5A). The addition of 20 mM CaCl\textsubscript{2} but not 20 mM MgCl\textsubscript{2} in the overlay medium containing 10 mM EDTA restored the binding of c95\textsubscript{A0B0} (Fig. 5A), indicating Ca\textsuperscript{2+} dependence of this binding. The binding of c95\textsubscript{A0B0} was also reduced by the presence of 0.5 mM NaCl (Fig. 5A). Finally, the binding of c95\textsubscript{A0B0} was inhibited by excess laminin-2, and, likewise, the binding of laminin-2 was inhibited by excess c95\textsubscript{A0B0} (Fig. 5B), indicating that the binding sites for agrin and laminin-2 overlap in Schwann cell α-dystroglycan.

To see if membrane proteins other than Schwann cell α-dystroglycan bind agrin and laminin-2 in peripheral nerve, we overlaid the nitrocellulose transfers of the crude bovine peripheral nerve membranes or the GlcNAc eluates of WGA chromatography of the crude bovine peripheral nerve membranes with c95\textsubscript{A0B0} or laminin-2. Both c95\textsubscript{A0B0} and laminin-2 bound to the 120-kDa smear, which was extracted from the membranes at pH 12 and enriched in the GlcNAc eluates of WGA chromatography (Fig. 6), indicating the specificity of the binding of agrin and laminin-2 to Schwann cell α-dystroglycan. Interestingly, a 30-kDa protein that remained in the pellets after pH 12 extraction and a 320-kDa protein that was enriched in the GlcNAc eluates bound laminin-2 but not c95\textsubscript{A0B0}, suggesting that Schwann cell α-dystroglycan is not the only peripheral nerve membrane protein that binds laminin-2.

Here we have demonstrated that 1) the peripheral nerve isoform of agrin is a 400-kDa component of the endoneurial basal lamina and is co-localized with α- and β-dystroglycan surrounding the outermost layer of myelin sheath of peripheral nerve fibers, 2) both endogenous peripheral nerve agrin and laminin-2 bind to Schwann cell α-dystroglycan, 3) the agrin C-terminal fragment lacking inserts at both A and B sites binds to Schwann cell α-dystroglycan in a Ca\textsuperscript{2+}-dependent manner, and 4) the binding sites for agrin and laminin-2 overlap in Schwann cell α-dystroglycan. In addition, this study is the first to demonstrate the binding of α-dystroglycan with both agrin and laminin-2 of the same tissue of the same species. Together with our previous report that laminin-2 is a ligand of the 120-kDa Schwann cell α-dystroglycan (11), these findings indicate that the 120 kDa α-dystroglycan is a dual receptor for agrin and laminin-2 in the Schwann cell membrane. This is in contrast to skeletal muscle, where agrin and laminin-2 are presumed to be the ligands of the 156-kDa α-dystroglycan in the neuromuscular junction and extrajunctional sarclemma, respectively (for a review see Ref. 23).

Thus far, the activity of agrin has been discussed only in terms of AChR clustering, and the biological functions of the agrin isoform lacking amino acid inserts at both A and B sites remain to be elucidated (23, 35). Together with the observation by Ruegg et al. (24), our results indicate that α-dystroglycan is a Schwann cell receptor of the agrin isoform inactive for AChR clustering. In the future, it is of utmost importance to clarify if peripheral nerve agrin has biological functions other than serving as a pure structural link between the endoneurial basal lamina and the Schwann cell membrane. It also awaits future
research to clarify how agrin and laminin-2 share α-dystroglycan molecules as their receptors in the Schwann cell membrane and what similar or different effects they have on the Schwann cell functions in vivo. In dy mice deficient in laminin α2 chain, muscle cell degeneration is uniformly observed, whereas dystromyelination is restricted to the proximal portion of peripheral nerve (36, 37). One possible mechanism for this difference is the absence of laminin-2 in dy peripheral nerve. Our results suggest that agrin may be such a molecule and also raise an intriguing possibility that like laminin-2, agrin may be involved in peripheral myelogenesis.

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