High Affinity Binding and Overlapping Localization of Neurocan and Phosphacan/Protein-tyrosine Phosphatase-ζ/β with Tenascin-R, Amphoterin, and the Heparin-binding Growth-associated Molecule*

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We have studied the interactions of the nervous tissue-specific chondroitin sulfate proteoglycans neurocan and phosphacan with the extracellular matrix protein tenascin-R and two heparin-binding proteins, amphoterin and the heparin-binding growth-associated molecule (HB-GAM), using a radioligand binding assay. Both proteoglycans show saturable, high affinity binding to tenascin-R with apparent dissociation constants in the 2–7 nM range. Binding is reversible, inhibited in the presence of unlabeled proteoglycan, and increased by ~60% following chondroitinase treatment of the proteoglycans, indicating that the interactions are mediated via the core (glyco)protein rather than by the glycosaminoglycan chains, which may in fact partially shield the binding sites. In contrast to their interactions with tenascin-C, in which binding was decreased by ~75% in the absence of calcium, binding of phosphacan to tenascin-R was not affected by the absence of divalent cations in the binding buffer, although there was a small but significant decrease in the absence of neurocan. Neurocan and phosphacan are also high affinity ligands of amphoterin and HB-GAM (Kd = 0.3–8 nM), two heparin-binding proteins that are developmentally regulated in brain and functionally involved in neurite outgrowth. The chondroitin sulfate chains on neurocan and phosphacan account for at least 80% of their binding to amphoterin and HB-GAM. The presence of amphoterin also produces a 5-fold increase in phosphacan binding to the neural cell adhesion molecule contactin. Immunocytochemical studies showed an overlapping localization of the proteoglycans and their ligands in the embryonic and postnatal brain, retina, and spinal cord. These studies have therefore revealed differences in the interactions of neurocan and phosphacan with the two major members of the tenascin family of extracellular matrix proteins, and also suggest that chondroitin sulfate proteoglycans play an important role in the binding and/or presentation of differentiation factors in the developing central nervous system.

In previous studies we have demonstrated that two nervous tissue-specific chondroitin sulfate proteoglycans, neurocan and phosphacan, are high affinity ligands of the extracellular matrix protein tenascin-C (1, 2) and of several neural cell adhesion molecules including Ng-CAM/L1, N-CAM, and TAG-1/aaxin-1 (3–5). Neurocan is synthesized by neurons (6), whereas phosphacan, which is produced by astrocytes (6), is an alternative splicing product representing the extracellular domain of a receptor-type protein-tyrosine phosphatase (7) that also occurs as a chondroitin sulfate proteoglycan in brain (8, 9). These interactions have dissociation constants in the range of 0.04–3 nM and in many cases are modulated by different types of proteoglycan glycosylation (5, 10).

Neurocan is a member of the family of hyaluronan-binding chondroitin sulfate proteoglycans that also includes aggrecan, versican, and brevican (11). All of these contain a lectin-like domain in their C-terminal portion, and a recombinant form of the lectin-like domain of versican specifically recognizes tenascin-R in blot overlay binding experiments using brain extracts (12). Tenascin-R has the same domain structure as tenascin-C and a similarly complex array of biological properties but has a more restricted localization, a different developmental time course, and is synthesized by oligodendrocytes and a subpopulation of neurons rather than predominantly by astroglia (13–15).

It has also recently been reported that phosphacan is a ligand of the heparin-binding growth-associated molecule (HB-GAM, also designated pleiotrophin) and that this interaction is mediated in part by the chondroitin sulfate chains of phosphacan (16). HB-GAM is an 18-kDa protein that was isolated from rat brain based on its neurite outgrowth promoting activity, and its expression in nervous tissue is developmentally regulated with the highest expression being during the perinatal period (17). HB-GAM contains a high proportion of basic amino acids, with lysine clusters at the N- and the C-terminal ends of the mature protein. It is homologous to the midkine proteins and the retinoic acid-inducible heparin-binding protein and thus forms a novel family of proteins structurally distinct from the fibroblast growth factors that may play a role in cell differentiation (18–20). The mitogenic activity of HB-GAM is questionable, and it is also likely that the mitogenic activity reported for pleiotrophin is due to contaminating heparin-binding growth-associated protein.

Amphoterin is another heparin-binding neurite outgrowth-
promoting protein with a molecular size of 30 kDa and is prominently expressed in embryonic brain. It is a highly charged molecule, but unlike HB-GAM and basic fibroblast growth factor amphoterin has a dipolar nature, characterized by a 184-amino acid cationic region followed by a cluster of 30 acidic residues. The primary structure of amphoterin is not related to the HB-GAM or fibroblast growth factor families of heparin-binding growth and/or differentiation factors, but amphoterin is homologous to one form of the HMG1-type DNA-binding protein (21). There is currently no evidence that amphoterin is involved in cell proliferation, and no enhancing or inhibitory effects were observed in standard mitogenic assays (22). Amphoterin has, however, recently been shown to bind specifically to the receptor for advanced glycation end products, a member of the immunoglobulin superfamily of cell surface molecules that is homologous to N-CAM, and amphoterin and the receptor for advanced glycation end products were found to be colocalized in the developing rat brain (23). Amphoterin has also been isolated recently from developing brain based on its ability to bind to oligosaccharides of sulfoglucuronyl glycolipids (24).

Although neurocan and phosphacan both interact with a number of cell adhesion and extracellular matrix proteins (1–5), distinctive properties of each proteoglycan, such as their relative affinity for different ligands, developmentally regulated proteolytic processing, and the effects on binding of chondroitin sulfate and N-linked oligosaccharides, are all capable of...
specifically modulating their interactions at different sites and periods with cell surface and extracellular matrix proteins (5, 10). In view of our previous demonstration of high affinity binding of neurocan and phosphacan to tenasin-C (1, 2), we have now studied the interactions of these two proteoglycans with the closely related molecule tenasin-R. The recent report of binding of HB-GAM/pleiotrophin to phosphacan (16) has also prompted us to compare its interactions with both neurocan and phosphacan and to examine their interactions with the related differentiation factor, amphoterin, on the premise that these proteins may also participate in proteoglycan-mediated regulation of cell adhesion, neurite growth, and cell migration during central nervous system development.

MATERIALS AND METHODS

Proteins and Antibodies—Neurocan and phosphacan (originally designated the 1D1 and 3F8 proteoglycans) were isolated from rat brain by ion exchange chromatography, gel filtration, and immunoadfinity chromatography (25), and tenasin-R was isolated from mouse brain by immunoadfinity chromatography as described by Pesheva et al. (26). Recombinant rat amphoterin and HB-GAM were expressed in baculovirus and purified as described previously (19, 22). Contactin was isolated from chicken brain by immunoadfinity chromatography (27). Neurotrimin was provided by Dr. James Salzer, N-cadherin by Dr. Gerald Grunwald, and other proteins were isolated or obtained from the sources described previously (5).

Polyclonal antisera to phosphacan (4) and to a recombinant glutathione S-transferase fusion protein containing a 22-kDa sequence from the nonhomologous chondroitin sulfate attachment domain of neurocan (5) were prepared as described previously. The 3F8 monoclonal antibody to phosphacan (25) and the 1F6 monoclonal antibody to an N-terminal epitope of neurocan (28) have also been described. Monoclonal and polyclonal antibodies to tenasin-R were prepared as described by Morganti et al. (29) and Pesheva et al. (30), respectively. Rabbit antisera to HB-GAM (anti-p18 peptide, Ref. 17) and amphoterin (anti-peptide II, Ref. 22) have been described previously.

Binding Assays—Neurocan and phosphacan were labeled to a specific activity of 1–10 \times 10^{18} \text{cpm/mol} with \text{[35S]}I by either the lactoperoxidase/glucose oxidase method using EnzymeBeads (Bio-Rad) or with the iodogen reagent (Pierce) according to the manufacturer’s instructions. Typically, 10–25 \mu g of protein were labeled per reaction, and free iodine was removed using a PD-10 column (Amersham Pharmacia Biotech).

To evaluate the effects on their binding properties of removing the chondroitin sulfate chains from neurocan and phosphacan, the labeled proteoglycans were treated for 1 h at 37 °C with protease-free chondroitin sulfate chains from neurocan and phosphacan, the labeled was removed using a PD-10 column (Amersham Pharmacia Biotech). of 0.5 unit/ml in 0.1M Tris-HCl buffer (pH 8.0), and completeness of digestion was confirmed by SDS-polyacrylamide gel electrophoresis on 10% gel and autoradiography of the resulting core glycoproteins.

Binding assays were performed as described previously (4). Briefly, proteins were coated in removable Immulon-4 wells, and binding of \text{[35S]}I-labeled neurocan and phosphacan was measured in 20 \text{mM Tris (pH 7.4)}, containing 150 \text{mM NaCl}, 2 \text{mM CaCl}_2, 2 \text{mM MgCl}_2, 0.02\% \text{NaN}_3, 0.25\% \text{NaN}_3, and 1 mg/ml heat-treated bovine serum albumin, following incubation with gentle shaking (45 rpm) for 3–12 h at room temperature. Reversibility of binding was demonstrated by incubation for varying periods in the presence of an excess of unlabeled proteoglycan (4). Scatchard plots were generated and dissociation constants were determined using the Macintosh version of the Ligand program (31).

RESULTS

Interactions with Tenasin-R—Radioligand binding assays demonstrated that the interaction of neurocan and phosphacan with tenasin-R reached equilibrium by ~9 h, resulting in 11 and 5% binding, respectively (Fig. 1). Binding was reversible (data not shown) and was inhibited in the presence of unlabeled proteoglycan (Fig. 1). Removal of the chondroitin sulfate chains by chondroitinase treatment of the proteoglycans in-
creased the binding of neurocan and phosphacan by ~60% (Fig. 2), indicating that the glycosaminoglycan chains are not directly involved in binding but may partially shield the binding sites on the proteoglycan core proteins. The effectiveness of the chondroitinase digestion was demonstrated by the shift of all 125I-labeled proteoglycan from the stacking gel to core proteins of the expected size in the separating gel following SDS-polyacrylamide gel electrophoresis and autoradiography (see “Materials and Methods”). Removal of N-linked oligosaccharides by treatment of tenascin-R with peptide N-glycosidase had no effect on its interactions with either neurocan or phosphacan (data not shown). Binding of phosphacan to tenascin-R was not affected by the absence of divalent cations in the binding buffer, whereas there was a small but significant decrease (24%) in the binding of neurocan (data not shown).

Binding of the proteoglycans to tenascin-R was saturable (Fig. 3), but there was a reproducible decrease in the binding of phosphacan at the highest concentration tested. Although we do not currently have a precise explanation for this particular phenomenon, it is evidently due to some peculiar interaction of high concentrations of these large (173 and ~200 kDa) multidomain proteins that are not commonly encountered with small ligands such as hormones, etc. Using the Marquardt-Levenberg algorithm (32) and Sigma-Plot (Jandel Scientific, San Rafael, CA) to perform a nonlinear regression analysis of the saturation data, we found that these experiments and those involving proteoglycan interactions with amphoterin and HB-GAM (see below) all fit a sigmoid model as required for valid Scatchard analysis of the data. The Scatchard plots generated by the Ligand program (31) indicated a single class of high affinity binding sites with apparent dissociation constants of ~7 and 2 nM for neurocan and phosphacan, respectively (Fig. 3). These affinities are on the same order of magnitude as those that we have previously determined for the binding of neurocan and phosphacan to tenascin-C (1, 2).

Immunocytochemical studies showed an overlapping localization of neurocan, phosphacan, and tenasin-R in the developing and adult central nervous system. Double immunofluorescence revealed strong neurocan and tenasin-R immunoreactivity in the outer plexiform layer (asterisk) of retina and to a lesser extent in the outer nuclear layer (onl) (Fig. 4, A and B). Similarly, there is a colocalization of phosphacan and tenasin-R in retina (Fig. 4, C and D) and optic nerve (Fig. 5).
Interactions with Amphoterin and HB-GAM—It has recently been reported (16) that phosphacan binds to HB-GAM, also known as pleiotrophin. We therefore compared the interactions of neurocan and phosphacan with HB-GAM and amphoterin, another heparin-binding protein that promotes neurite outgrowth. Neurocan and phosphacan both bind reversibly to amphoterin and HB-GAM (Fig. 5), and binding is inhibited by unlabeled proteoglycan (Fig. 5) and greatly reduced by chondroitinase treatment (Fig. 6). Chondroitin sulfate (at a maximum tested concentration of 1.2 μM) inhibited the binding of neurocan to amphoterin and HB-GAM by 35–45%, and phosphacan binding to HB-GAM was inhibited by 48% and to amphoterin by 76% (data not shown). Saturation studies and Scatchard analysis demonstrated that the apparent binding affinity of phosphacan to both proteins (Kd = 0.3–0.8 nM; Fig. 7) is an order of magnitude greater than that of neurocan (Kd = 1–8 nM; Fig. 8).

Although expression cloning has identified the neural cell adhesion molecule contactin/F3/F11 as a ligand for recombinant forms of phosphacan/protein-tyrosine phosphatase-ζ (33, 34), using native phosphacan and contactin we detected only minimal binding of these proteins (Fig. 9). It was therefore of interest to examine the question of whether any of the other phosphacan ligands that are present in nervous tissue together with contactin would affect phosphacan-contactin interactions (e.g. by acting as a "coreceptor"). These experiments demonstrated that in the presence of amphoterin, binding of phosphacan to contactin is increased 5-fold. A smaller (2–3-fold) increase was seen in combination with tenascin-C and tenasin-R, whereas addition of HB-GAM increased binding by only 1.6-fold, and no significant potentiating effect was seen with other high affinity ligands of phosphacan (11), such as the neural cell adhesion molecules Ng-CAM, Nr-CAM, axonin-1, and N-CAM (Fig. 9). Like the binding of phosphacan to amphoterin itself, the potentiating effect of amphoterin on phosphacan binding to contactin was essentially abolished after chondroitinase treatment of the proteoglycan, emphasizing the importance of the chondroitin sulfate chains in phosphacan-amphoterin interactions.

Immunocytochemical studies revealed that as in the case of tenasin-R, there is an overlapping localization of neurocan and phosphacan with amphoterin in the embryonic brain and spinal cord and in postnatal cerebellum and retina. For neurocan this was seen in the ventricular and marginal zones of E13 brain, throughout the developing spinal cord and in the dorsal root ganglion, and in the adult optic nerve and retina (data not shown). Colocalization of amphoterin and phosphacan was seen in the dorsal root entry zone (asterisk), mantle layer (ml), neuroepithelium (ne), and the dorsal root ganglion (drg) of E13 spinal cord (Fig. 10, A and B), in the adult retina (Fig. 10, C and D), and in the molecular layer (ml) and surrounding the Golgi epithelial cells (arrows) of the cerebellum (Fig. 10, E and F). The localization of neurocan and phosphacan also corresponds to many areas in which HB-GAM is present (20, 28, 35, 36, and data not shown).

**DISCUSSION**

Earlier studies have shown that neurocan and phosphacan bind to the greatest extent and with the highest affinities to a variety of immunoglobulin superfamily neural cell adhesion molecules, including Ng-CAM/L1, N-CAM, Nr-CAM, and TAG-1/axonin-1 (3–5). Binding to these proteins usually amounts to 35–40% of the input radioactivity in radioligand binding assays (Fig. 11), with apparent dissociation constants in the subnanomolar range. There is also detectable but considerably less binding of neurocan and phosphacan to contactin, whereas no binding was observed to two other immunoglobulin superfamily neural cell adhesion molecules, the myelin-associated glycoprotein and neurotrimin. Other high affinity ligands of these proteoglycans are tenasin-C (1, 2) and tenasin-R, as described in this report. Binding of neurocan and phosphacan to both tenascins has the same apparent Kd of ~3 nM, but the affinities and the percent of the input protein that is bound are significantly less than the corresponding values determined for their interactions with neural cell adhesion molecules. However, the neural cell adhesion molecules and tenascins represent the major ligands that have been identified up to now, insofar as no significant binding was observed to a number of other cell surface and extracellular matrix proteins such as N-cadherin, fibronectin, vitronectin, merosin, thrombospondin, the epidermal growth factor and basic fibroblast growth factor receptors, and (at least in the case of phosphacan) collagens I–VI and laminin (Fig. 11).

Using an affinity matrix containing the N-terminal cysteine-rich sequence and the epidermal growth factor-like repeats of tenasin-R expressed as a glutathione-S-transferase fusion protein, Xiao et al. (37) have isolated from a mouse brain extract a chondroitin sulfate proteoglycan with biochemical and immunochemical properties resembling those of phospha-
Although binding to the epidermal growth factor-like domain was calcium-dependent, in the present study the absence of calcium had no significant effect on the binding of phosphacan to native tenascin-R. These results with respect to tenascin-R differ from those previously obtained for both phosphacan and neurocan binding to tenascin-C, in which binding was decreased by 75% in the absence of calcium and magnesium (2, 10). The involvement of the epidermal growth factor-like domain in the binding of phosphacan to tenascin-R also differs from the situation with respect to phosphacan and neurocan interactions with tenascin-C, where binding is mediated by the fibronectin-like globule, and in the case of neurocan is also influenced by the presence or absence of the adjacent fibronectin type III repeats (2). However, because there is only ~62% amino acid sequence identity in the fibronectin-like domains of tenascin-C and tenascin-R, this domain of tenascin-R may not have the same binding properties as the fibronectin globule of tenascin-C. It has also recently been found that the C-terminal half of neurocan binds to fibronectin type III repeats 4 and 5 of ...
were coated at 10 mg/ml concentration of 1 ng/ml, showing a high percentage of binding at equilibrium, 4–24 h), proteins of this binding activity (Maeda et al. (16) found that chondroitinase treatment to remove the glycosaminoglycan chains, indicating that chondroitin sulfate is the major mediator of their binding to these proteins. Maeda et al. (16) found that chondroitinase treatment of 125I-labeled phosphacan reduced its binding to HB-GAM by only 40%, a result that might be due to the different procedures used for iodination of phosphacan or to differences in the phosphacan preparations, binding assays, the completeness of chondroitinase digestion, or in the source of HB-GAM. These investigators also reported that their Scatchard analysis of phosphacan binding to HB-GAM indicated the presence of two binding sites with different affinities and that chondroitin 6-sulfate was a much more potent inhibitor of binding than chondroitin 4-sulfate. In view of our previous demonstration of developmental changes in the sulfation of chondroitin sulfate chains on phosphacan (25), they suggested that this developmental change in sulfation may modulate phosphacan binding to HB-GAM. However, saturation curves and Scatchard analysis of the binding of phosphacan from 7-day postnatal brain (containing 67% chondroitin 4-sulfate and 33% chondroitin 6-sulfate) showed no significant difference in affinity as compared with the binding of phosphacan isolated from adult brain, containing 96% chondroitin 4-sulfate and <4% chondroitin 6-sulfate (data not shown).

Although visual inspection of our Scatchard plot of phosphacan/HB-GAM interactions (Fig. 7) suggests the possibility of two binding sites, the data analysis program that we used (31), in which the parameters are estimated by means of a weighted nonlinear least squares algorithm, does not accept a model with two binding sites. However, linear curve fitting using the Deltagraph program (DeltaPoint Inc., Monterey, CA) yielded dissociation constants of 0.12 and 3.6 nM, which are very similar to the values of 0.25 and 3 nM reported by Maeda et al. (16) for the binding of phosphacan from 16 day postnatal brain to HB-GAM. Linear curve fitting was also performed for the interactions of neurocan and phosphacan with tenascin-R (Fig. 3). In these cases also the Ligand program did not accept a model with two binding sites, but using Deltagraph dissociation constants of 0.97 and 10.5 nM could be calculated for the neurocan/tenascin-R interaction and 0.35 and 4.3 nM for binding of phosphacan to tenascin-R. Whether one considers the one- or the two-component model most reliable, it is clear from our data that the binding is of high affinity, with dissociation constants in the 0.1 to 10 nM range.

In all cases we found that there is an overlapping localization in the central nervous system of neurocan and phosphacan with tenascin-R, amphoterin, and HB-GAM, which fulfills a basic condition for the biological significance of their high affinity interactions demonstrated in radioligand binding assays.

Our previous studies have demonstrated the interactions of neurocan and phosphacan with several neural cell adhesion molecules and extracellular matrix proteins (1–5, 10), all of which are large modular proteins with multiple domains. The report by Maeda et al. (16) and the present study now identify a new class of ligands for neurocan and phosphacan which shares a high affinity for heparin and promotes neurite outgrowth. HB-GAM and amphoterin are small proteins that are rich in basic amino acids, and although they lack the modular organization of the neural cell adhesion molecules and tenascins, they are associated with the extracellular matrix of nervous tissue where they are thought to be involved in developmental and regenerative processes and in neurite growth. Because amphoterin forms dimers and possibly higher oligomers under physiological conditions (38) and produces a 5-fold increase in the binding of phosphacan to contactin (Fig. 9), it is possible that it may serve to link phosphacan in the extracellular matrix, or the transmembrane phosphatase on adjacent cells, to cell surface glycoproteins such as contactin to which phosphacan alone binds only minimally.

The result of neurocan and phosphacan interactions with amphoterin and HB-GAM is, however, likely to differ in most respects from the consequences of proteoglycan binding to neural cell adhesion molecules and extracellular matrix proteins.
involved in cell-cell and cell-matrix interactions during nervous tissue histogenesis. Rather, it is more probable that by virtue of their ability to bind amphoterin and HB-GAM, neurcan, and/or phosphacan may be involved in the storage, release, or presentation of these differentiation factors to cells in a process analogous to that whereby heparan sulfate proteoglycans mediate the actions of basic fibroblast growth factor. Although most studies of growth factor interactions with proteoglycans have concerned heparan sulfate proteoglycans and more specifically their glycosaminoglycan chains, it would appear that the interactions of chondroitin sulfate proteoglycans with differentiation factors may also play a significant role in developmental processes.

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