Association of p75NTR with Caveolin and Localization of Neurotrophin-induced Sphingomyelin Hydrolysis to Caveolae*

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Caveolae are plasma membrane microdomains that are enriched in caveolin, the structural protein of caveolin, sphingomyelin, and other signaling molecules. We previously suggested that neurotrophin-induced p75NTR-dependent sphingomyelin hydrolysis may be localized to the plasma membrane. Therefore, we examined if caveolae were a major site of p75NTR-dependent sphingomyelin hydrolysis in p75NTR NIH 3T3 fibroblasts. Caveolin-enriched membranes (CEMs) were prepared by either detergent or detergent-free extraction and separated from noncaveolar membranes by centrifugation through sucrose gradients. Immunoblot analysis of the individual gradient fractions indicated that caveolin and p75NTR were enriched in CEMs. The localization of p75NTR to CEMs was not an artifact of receptor overexpression in the fibroblasts because a similar distribution of p75NTR was evident from PC12 cells, which endogenously express p75NTR. In the p75NTR fibroblasts, neuro growth factor induced a time-dependent hydrolysis of sphingomyelin only in CEMs with no hydrolysis detected in noncaveolar membranes. Intriguingly, endogenous p75NTR was found to co-immunoprecipitate with caveolin, suggesting that p75NTR may associate with caveolin in vitro. This interaction was confirmed in vitro by the co-immunoprecipitation of a glutathione S-transferase fusion protein expressing the cytoplasmic domain of p75NTR with caveolin. Collectively, these results demonstrate that neurotrophin-induced p75NTR-dependent sphingomyelin hydrolysis localizes to CEMs and suggest that the interaction of p75NTR with caveolin may affect signaling through p75NTR.

The neurotrophins are a family of growth factors involved in the survival, development, and death of specific populations of neurons and glial cells (1). The signal transduction systems that mediate these divergent biologies are initiated by the interaction of neurotrophins with two classes of cell surface receptors (2). Many of the trophic signals elicited by neurotrophins are initiated by the binding of these molecules to various Trk tyrosine kinase receptors (3–9). In contrast, recent data suggest that neurotrophin-mediated death signals are generated through the interaction of nerve growth factor (NGF)1 with a transmembrane protein known as the low affinity neurotrophin receptor, p75NTR (10–12). Although the signaling mechanisms used by p75NTR are still uncertain, we have demonstrated that p75NTR couples to sphingomyelin (SM) hydrolysis, producing the bioactive sphingolipid metabolite ceramide (13, 14).

Ceramide production following ligand binding of p75NTR has been implicated in antiproliferative responses in glial cells (15). For example, exogenous ceramide mimicked the effect of NGF on cell growth inhibition and differentiation of rat T9 glioma cells (13). Additionally, NGF-induced p75NTR-dependent apoptosis correlates with an early and prolonged increase in cellular ceramide levels in mature oligodendrocytes (10). Further, NGF-induced p75NTR-dependent ceramide production has been implicated in regulating dopamine release in primary cultures of mesencephalic neurons (16).

The coupling of p75NTR to ceramide production and the emerging role of this receptor-effector system in glial and neuronal biologies necessitates the identification of the signal-sensitive pool of lipid, localization of the specific compartment for signal generation/regeneration, and defining the site of interaction with potential downstream effector molecules.

Previous studies have suggested that ligand-induced SM hydrolysis may use a plasma membrane pool of SM, which is not effected by treatments that inhibit receptor internalization (14, 17, 18). Caveolae are dynamic microdomains of the plasma membrane that are enriched in SM and remain associated with the cell surface (19), suggesting that caveolae may be localized sites for ligand-induced SM hydrolysis. Indeed, interleukin-1β treatment of dermal fibroblasts induced SM hydrolysis and ceramide generation within caveolae (20). Moreover, caveolae have been implicated as sites for signal transduction via the epidermal growth factor and platelet-derived growth factor receptors (21, 22). Thus, caveolae are emerging as important signaling compartments within the plasma membrane (23).

Caveolin is the major protein component of caveolae and is necessary for formation of intact caveolae (23). Caveolin serves as a scaffolding protein (24) involved in sequestering pools of G-proteins (25), Ras (26), and other effector molecules (21, 22, 27). Moreover, caveolin can interact with proteins in a very specific manner such that only inactive forms of G-proteins are found associated with caveolin (25). Thus, caveolin may be an important component of receptor-effector systems localized within caveolae.

The abundance of SM within caveolae and the role of caveolin in sequestering signaling molecules led us to examine if p75NTR-dependent SM hydrolysis localized to caveolae and if this receptor interacted with signaling. We demonstrate herein that p75NTR and caveolin co-localize and that p75NTR-dependent SM hydrolysis occurs within CEMs. Further, p75NTR was found to co-immunoprecipitate with caveolin from CEMs. Collectively, these results suggest that caveolae may provide a highly localized site for neurotrophin-induced SM hydrolysis.

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1 The abbreviations used are: NGF, nerve growth factor; CEM, caveolin enriched membrane; NCM, noncaveolar membrane; MES, 2-(4-morpholinio)ethanesulfonic acid; GST, glutathione S-transferase; SM, sphingomyelin; PAG, polyacrylamide gel electrophoresis.
and that the association of p75\textsuperscript{NTR} with caveolin may have a functional role in neurotrophin signaling through p75\textsuperscript{NTR}.

**EXPERIMENTAL PROCEDURES**

**Materials**—Mouse 2.5 S NGF was obtained from Harlan Bioproducts for Science. [\textsuperscript{3}H]Choline chloride (86 Ci/mmol) was purchased from American Radiolabeled Chemicals. Polyvalent anti-caveolin antibodies were products of Signal Transduction Labs. Anti-GST monoclonal antibody was obtained from Santa Cruz Biotechnology. Anti-p75\textsuperscript{NTR} antibody 9991 (13) and the GST-p75\textsuperscript{NTR} fusion protein expressing the cytoplasmic domain of p75\textsuperscript{NTR} were generously provided by Dr. Moses Chao. Protein A-Sepharose and glutathione-Sepharose were from Pharmacia Biotech Inc. All tissue culture media and geneticin were products of Life Technologies, Inc.

**Cell Lines**—The production and characterization of the p75\textsuperscript{NTR}-NIH 3T3 cells has been previously described (29), p75\textsuperscript{NTR}-NIH 3T3 and PC12 cells were cultured as described (14). NIH 3T3 cells stably transfected with a pCMV vector lacking the p75\textsuperscript{NTR} cDNA insert were maintained in Dulbecco's modified Eagle's medium/10% fetal calf serum containing 0.2 mg/ml geneticin. All cells were maintained at 37 °C in a humidified atmosphere containing 5% CO\textsubscript{2}.

**Isolation of CEMs**—CEMs were prepared by either detergent or nondetergent extraction of cell proteins and centrifugation over discontinuous sucrose gradients essentially as described (26, 30). Cells were grown in 15-cm tissue culture dishes, and two dishes of cells were used for each experiment. Aliquots of 0.4 ml of 38% sucrose and 0.4 ml of 5% sucrose (both in MBS) were added to each dish of cells. The dishes were incubated for 20 h at 4 °C and 15 × 0.8 ml fractions were collected manually from the top of the gradient. Aliquots of each fraction were used for the determination of protein content (31).

To determine the distribution of p75\textsuperscript{NTR} and caveolin within the gradient, 0.075 ml of each fraction were subjected to SDS-PAGE on 10 or 12% acrylamide gels followed by immunoblotting. Following SDS-PAGE, the proteins were transferred to nitrocellulose, and the membranes were stained with 0.5% Ponceau S to visualize total protein. As described previously (30), the bulk of the cellular proteins remained in fractions 10–15 of the gradient (data not shown). The membrane was typically cut in half at about the 44-kDa molecular mass marker, and the upper half of the blot was used to probe for p75\textsuperscript{NTR} (75 kDa), and the lower half of the blot was used to probe for caveolin (22–24 kDa). Proteins were visualized using enhanced chemiluminescence (Amer sham, Corp.).

In some experiments, CEMs were prepared by nondetergent extraction with sodium carbonate (26). Detergent-free extraction of the cells was performed as above with the following modifications. The cells were scraped into 2 ml of 0.5 M sodium carbonate, pH 11, and homogenization was carried out sequentially with a loose fitting Dounce homogenizer (20 strokes). The extract was adjusted to 40% sucrose by the addition of 2 ml of 80% sucrose in MBS lacking Triton X-100 and placed in the bottom of an ultracentrifuge tube. A discontinuous sucrose gradient was formed by overlaying this solution with 4 ml of 38% sucrose and 4 ml of 5% sucrose (both in MBS). The tubes were centrifuged at 31,000 rpm in a SW41 rotor for 16–18 h at 4 °C and 15 × 0.8 ml fractions were collected manually from the top of the gradient. Aliquots of each fraction were used for the determination of protein content (31).

**Metabolic Labeling and Sphingomyelin Measurements**—Cellular SM pools were labeled with [\textsuperscript{3}H]choline, and SM was quantitated as described previously (14).

**RESULTS AND DISCUSSION**

**p75\textsuperscript{NTR} Co-migrates with Caveolin**—To determine if a pool of p75\textsuperscript{NTR} may localize to CEMs, we studied p75\textsuperscript{NTR}-NIH 3T3 cells to sodium carbonate extraction and analyzed the individual gradient fractions for the distribution of p75\textsuperscript{NTR} and caveolin. Immunoblot analysis for p75\textsuperscript{NTR} and caveolin revealed that a large pool of p75\textsuperscript{NTR} co-migrated with caveolin (Fig. 1).

Because fibroblasts do not endogenously express p75\textsuperscript{NTR}, it was possible that the presence of p75\textsuperscript{NTR} in CEMs was an artifact of receptor overexpression in the fibroblasts. Therefore, we determined whether p75\textsuperscript{NTR} co-localized with CEMs isolated from PC12 cells, which endogenously express p75\textsuperscript{NTR}. Fractionation of PC12 cells under the above conditions resulted in a similar distribution of p75\textsuperscript{NTR} within the gradient (Fig. 2). However, immunoblot analysis did not detect caveolin, indicating that PC12 cells either do not express caveolin or that they express an isoform not recognized by the polyclonal antibody used in these experiments. The sedimentation of the membranes within this area of the sucrose gradient is indicative of a high buoyant density, suggesting that a pool of p75\textsuperscript{NTR} associates with areas of the membrane enriched in glyco-sphingolipids but not necessarily enriched in caveolin (33).

Interestingly, detergent extraction of either the p75\textsuperscript{NTR}-NIH 3T3 fibroblasts or the PC12 cells resulted in less p75\textsuperscript{NTR} migrating in fractions 4–7 than was apparent under conditions of detergent-free extraction (data not shown). However, in the fibroblasts, caveolin still primarily migrated to fractions 4–7 due to the marked insolubility of this protein in Triton X-100 (33). Differences in the amount of p75\textsuperscript{NTR} co-migrating with CEMs under conditions of detergent versus detergent-free extraction may be due to detergent solubilization of a palmitoylated form of p75\textsuperscript{NTR} (35). Previous studies have identified that detergent extraction results in the loss of other lipid-modified proteins from CEMs (26). In contrast, detergent-free extraction of the cells with sodium carbonate facilitates the recovery of lipid-modified proteins within CEMs (26, 34). Indeed, labeling of the p75\textsuperscript{NTR} fibroblasts with [\textsuperscript{3}H]palmitate followed by detergent extraction resulted in the majority of palmitoylated p75\textsuperscript{NTR} migrating in fractions 9–15, suggesting that detergent extraction may affect the partitioning of p75\textsuperscript{NTR} between CEMs and NCMs (data not shown).

**Neurotrophins Induce Sphingomyelin Hydrolysis within CEMs**—We have previously reported that neurotrophins hydrolyze an internal pool of SM (14). Because the CEMs are enriched in SM (19, 20) and contain a significant pool of SM, we asked whether neurotrophin-induced SM hydrolysis is localized to this pool of the plasma membrane. We treated p75\textsuperscript{NTR} NIH 3T3 fibroblasts with phosphate-buffered saline or NGF, detergent-extracted the cells, and fractionated the membranes as above. The majority of the SM (47%) migrated in fractions 4–7, with the remainder primarily distributed to fractions 12–15 (35%). However, analysis of the amount of SM within each fraction revealed that NGF hydrolyzed SM solely in the CEMs, fractions 4–7 (Fig. 3).
To determine if the method of preparation of CEMs had any effect on the distribution of the neurotrophin sensitive pool of SM, we treated [3H]choline-labeled cells with phosphate-buffered saline or 100 ng/ml NGF for 12 min in a 37 °C water bath, and then the cells were subjected to detergent extraction. Identical amounts of protein from control and treated cells were loaded on discontinuous sucrose gradients, and membrane fractions were isolated as described under "Experimental Procedures." Individual fractions of 0.8 ml were manually recovered from the top of the gradient and assessed for protein and SM content. SM levels were normalized to total protein within each fraction, and the results were expressed as the percentage of control levels of SM from the same fraction. The data shown are the mean ± S.D. from three experiments.

| Time | Total sphingomyelin recovered | Sphingomyelin hydrolyzed |
|------|--------------------------------|--------------------------|
|      | CEMs | NCM-1 | NCM-2 | CEMs | NCM-1 | NCM-2 |
| min  |      |       |       |      |       |       |
| 8    | 93.7 | 4.3   | 2.0   | 8.5  | 1.8   | 0     |
| 10   | 95.4 | 4.0   | 0.6   | 17.3 | 2.1   | 0.4   |
| 12   | 95.1 | 3.6   | 1.3   | 19.0 | 2.1   | 0.36  |
| 15   | 94.2 | 4.7   | 1.1   | 12.3 | 1.9   | 0.34  |

Some signaling proteins, i.e. Ras and G-proteins (25, 26, 34), and form a high molecular weight complex composed of caveolin homologomers (24). These observations, together with the results described above, led us to investigate whether p75<sup>NTR</sup> may directly interact with caveolin.

The p75<sup>NTR</sup>-NIH 3T3 fibroblasts were subjected to detergent-free extraction, and the membranes were separated over the sucrose gradient as described. Based upon the fractionation pattern of p75<sup>NTR</sup> shown in Fig. 1, the individual fractions were
The figure is a composite of these the two immunoblots for p75NTR complexes were formed, and the bound proteins were resolved by SDS-PAGE (fractions 12–15). Fractions 1–3 were discarded, combined into CEMs (fractions 4–7), NCM-1 (fractions 8–11), and NCM-2 (fractions 12–15). The gel shown is identical to results obtained in three experiments.

Importantly, the caveolin antibody did not immunoprecipitate any caveolin nor p75NTR from membranes isolated from fractions 4–7 from PC12 cells (Fig. 4A). Because PC12 cells do not express any proteins recognized by the caveolin antibody, these results indicate that p75NTR was not nonspecifically associating with the antibody. Additionally, the caveolin antibody did not co-immunoprecipitate p75NTR from CEMs nor NCMS isolated from mock transfected fibroblasts, strongly supporting that caveolin can specifically associate with p75NTR in cells expressing both caveolin and p75NTR (Fig. 4B).

To further confirm that p75NTR could associate with caveolin, we examined the ability of a GST-p75NTR fusion protein expressing the full-length cytoplasmic domain of p75NTR to associate with caveolin in vitro. CEMs isolated from mock transfected NIH 3T3 fibroblasts were incubated with 0 or 30 μg of the GST-p75NTR fusion protein. Subsequently, caveolin was immunoprecipitated with a polyclonal caveolin antibody. After formation of the immune complexes with protein A-Sepharose, the bound proteins were solubilized and resolved by SDS-PAGE. The proteins were transferred to nitrocellulose, the blots were cut in half just above the 32-kDa molecular marker, and the upper half of the blot was probed with either the p75NTR antisera (Fig. 5A) or a monoclonal antibody against the GST affinity handle (Fig. 5B). In both panels, the lower portion of the blots were probed with the anti-caveolin antibody. Fig. 5 (A and B) shows that the caveolin antibody co-immunoprecipitated the GST-p75NTR fusion protein as detected using either the p75NTR antisera or the GST affinity gene. As expected, caveolin was equally immunoprecipitated in all instances. Importantly, the caveolin antibody did not co-immunoprecipitate any p75NTR or GST immunoreactive bands from CEMs incubated with GST only (Fig. 5C). Thus, co-immunoprecipitation of the GST-p75NTR fusion protein with caveolin was not mediated by an interaction between caveolin and the GST affinity handle. Collectively, these results strongly support that caveolin can directly associate with a region within the cytoplasmic domain of p75NTR.

Caveolae are emerging as highly localized sites for lipid signaling events. Indeed, recent results indicate that epidermal growth factor-induced hydrolysis of phosphatidylinositol-bisphosphate also occurs solely within CEMs from A431 cells (36). Moreover, caveolae may serve as sites for cross-talk between tyrosine kinase and lipid signaling pathways. Because signaling via the epidermal growth factor and platelet-derived growth factor receptors occurs within CEMs (21, 22), other receptor-linked tyrosine kinases may be resident in CEMs. These results raise the possibility that localization of p75NTR signaling to CEMs may have functional significance for cross-talk between Trk and p75NTR signaling pathways. We and others have reported that activation of Trk tyrosine kinases can inhibit p75NTR-dependent SM hydrolysis and ceramide generation (14,16). Therefore, co-localization of p75NTR with...
Trk receptors within caveolae may enrich p75NTR in an area of the plasma membrane where it can effectively couple to its putative effector system (SM hydrolysis/ceramide generation) or interact with the Trk effector system. p75NTR has been demonstrated to associate with the 42- and 44-kDa forms of mitogen activated protein kinase (37), an undefined 120/104-kDa kinase (38), and two unidentified phosphoproteins of 60 and 130 kDa (39). However, the role of these proteins in p75NTR signaling remains unknown. The role of caveolin as a scaffolding protein involved in organizing and sequestering signaling molecules within caveolae (23, 24) suggests that the association of caveolin with p75NTR may have functional consequences for p75NTR signaling. For example, the association of p75NTR with caveolin may directly or indirectly...
impair specificity to neurotrophin signaling through p75\(_{NTR}\). Recent results indicate that NGF but not BDNF nor neurotrophin-3 can activate NF-\(\kappa\)B in primary cultures of Schwann cells (40) and induce apoptosis in primary cultures of mature oligodendrocytes (10). Presumably, both of these effects are mediated through NGF-induced p75\(_{NTR}\)-dependent ceramide generation. Thus, although all the neurotrophins can couple to SM impart specificity to neurotrophin signaling through p75\(_{NTR}\).

In conclusion, the localization of p75\(_{NTR}\)-dependent SM hydrolysis to CEMs extends our previous observations on p75\(_{NTR}\) signaling through SM metabolism and in the broader perspective implicates caveolin as a potentially important component in affecting cellular responses to neurotrophins through p75\(_{NTR}\).

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