NCAM plays a key role in neural development and plasticity-mediating cell adhesion and differentiation mainly through homophilic binding. Until recently, attempts to modulate neuronal differentiation and plasticity through NCAM have been impeded by the absence of small synthetic agonists mimicking homophilic interactions of NCAM. We show here that a peptide, P2, corresponding to a 12-amino acid sequence localized in the FG loop of the second Ig module of NCAM, binds to the first Ig module, which is the natural binding partner of the second Ig module, with an apparent $K_d$ of $4.7 \pm 0.9 \times 10^{-7}$ M. P2 inhibits cell aggregation and induces neurite outgrowth from hippocampal neurons, maximal neuritogenic effect being obtained at a concentration of 0.8 $\mu$M. The neuritogenic effect was inhibited by preincubation with P2 with the recombinant NCAM-IgI. Both the length of P2 and the basic amino acid residues at the N and C termini are important for its neuritogenic activity. Treatment of hippocampal cultures with P2 results in induction of phosphorylation of the mitogen-activated protein kinases ERK1 and ERK2. Thus, P2 is a potent mimetic of NCAM, and therefore, an attractive compound for the development of drugs for the treatment of neurodegenerative diseases.

The neural cell adhesion molecule (NCAM) is a cell surface glycoprotein that belongs to the Ig superfamily. NCAM is primarily expressed in neurons, glial cells, and skeletal muscle. Alternative splicing of mRNA transcribed from a single gene generates three major NCAM isoforms: NCAM-A (180 kDa), NCAM-B (140 kDa), and NCAM-C (120 kDa). These isoforms have identical extracellular parts consisting of five N-terminal Ig-like modules (IgI–IgV) followed by two fibronectin type III modules (1). The transmembrane isoforms, NCAM-A and NCAM-B, have intracellular parts of different sizes, whereas NCAM-C is linked to the cell membrane via a glycosylphosphatidylinositol anchor. NCAM is known to mediate Ca$^{2+}$-independent cell-cell and cell-substratum adhesion via homophilic (NCAM binding to NCAM) and heterophilic (e.g. NCAM binding to heparin/heparan sulfate proteoglycans) interactions, respectively (2–4). NCAM homophilic binding was originally reported to depend on a reciprocal interaction involving IgIII modules of two opposing NCAM molecules (5, 6). Later, an interaction involving all five Ig modules was also suggested (7). A double reciprocal binding between the recombinant IgI and IgII modules was demonstrated by means of surface plasmon resonance analysis (8), and recently, the three-dimensional structure of the IgI and IgIIIIII modules of rat NCAM was determined by both NMR spectroscopy and x-ray crystallography, resulting in the identification of homophilic binding sites in the IgI and IgII modules (9, 10).

Neurons have been shown to respond with an increased neurite outgrowth to both glycosylphosphatidylinositol-linked and transmembrane isoforms of NCAM expressed on the surface of non-neuronal cells (11). NCAM homophilic binding has been suggested to activate the fibroblast growth factor receptor-signal-pathway (12, 13), and recently, the Ras mitogen-activated protein kinase (Ras-MAPK) signaling pathway has also been implicated in NCAM-dependent neurite outgrowth (14, 15).

As mentioned above, the IgII module of NCAM has been identified as a natural ligand of the IgI module (8) and shown to induce NCAM-specific neurite outgrowth (16). Therefore, we decided to design a putative peptide ligand of NCAM based on our knowledge of the structure of the homophilic binding site localized in IgII. In this study, we demonstrate that a peptide corresponding to a 12-amino acid sequence of the FG loop of the second Ig module of NCAM binds to the first Ig module, inhibits cell aggregation, activates the mitogen-activated protein kinase (MAPK) pathway, and stimulates neurite outgrowth in primary cultures of rat hippocampal neurons. Thus, based on current knowledge of the three-dimensional structure of homophilic binding sites in NCAM, we have identified a small peptide mimetic of NCAM with strong neuritogenic activity. This approach not only opens up new possibilities in studying the role of NCAM in neuronal differentiation and plasticity but may also allow the development of new tools potentially useful for the treatment of neurodegenerative disorders.

**EXPERIMENTAL PROCEDURES**

**Materials**—The MEK1/2 inhibitor U0126 was purchased from Promega (Madison, WI). Rabbit anti-rat GAP-43 antibodies were from Chemicon International (Temecula, CA).

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Preparation of Peptides—Peptides were synthesized using the Fmoc protection strategy on TentaGel resin (Rapp Polymere, Tübingen, Germany) using Fmoc- (Calbiochem-Novabiochem) protected amino acids. Dendrimers were composed of four monomers coupled to a lysine backbone. All concentrations of the P2 and C3 dendrimers (P2d and C3d, respectively) were calculated based on the amount of monomers. Peptides were at least 95% pure as estimated by high performance liquid chromatography and matrix-assisted laser desorption/ionization time-of-flight mass spectroscopy. The purity of the recombinant proteins was at least 95%, as estimated by SDS-PAGE. Folding of the recombinant IgI and IgII modules was established by one- and two-dimensional NMR spectra.

Surface Plasmon Resonance Analysis—Real-time biomolecular interaction (surface plasmon resonance) analysis was performed using the BIACore-X instrument (Biacore AB, Uppsala, Sweden) as follows: 4000 resonance units of P2 peptide dendrimers were immobilized noncovalently on a CM5 sensor chip (Biacore AB) by electrostatic precocentration. Binding of the recombinant IgI and IgII modules of NCAM in the 12.5–100 μM concentration range was measured at 25 °C in HEPES-buffered saline (10 mM HEPES, pH 7.4, 150 mM NaCl, 3.4 mM EDTA, 0.005% w/v Surfactant P20 (Biacore AB)) at a flow rate of 10 μl/min. After each binding cycle, the sensor chip was regenerated by three 8-μl injections of 50 mM NaOH. Data were analyzed by nonlinear curve fitting using the BIACevaluation software version 2.2.4 (Biacore AB). Models of single-site binding association and dissociation were used to derive the apparent association and dissociation rate constants. Three independent experiments were performed.

Primary Cultures of Hippocampal Neurons—Hippocampi were isolated from Wistar rat embryos at gestational day 18, and dissociated cells were obtained as described previously (18). Briefly, isolated hippocampal tissue was homogenized, trypsinized, and incubated in the presence of DNase I (Sigma) and soybean trypsin inhibitor (Sigma). For microwell aggregation cultures, cells were seeded in 60-well microtiter plates (NUNC, Roskilde, Denmark) at a density of 50,000 cells/well in a volume of 15 μl. For low density cultures, dissociated neurons were seeded in 8-well LabTek coverslides (NUNC) at a density of 5000 cells/cm². Cultures were maintained at 37 °C, 5% CO₂ in Neurobasal medium supplemented with B27, 4 mg/ml bovine serum albumin, 100 units/ml penicillin, and 100 μg/ml streptomycin (all from Invitrogen). The recombinant Ig modules of NCAM and synthetic peptides were added to the medium immediately after plating.

Cell Aggregation and Neurite Outgrowth Assays—Microwell aggregation cultures and coverslides were examined under a Nikon Diaphot 300 inverted microscope using Nikon Plan ×20 phase-contrast optics. Video recordings were made with a Videotech video camera (Grundig Electronics, Germany). 768 × 576 pixel images were stored using the PRIGRA software package (Protein Laboratory, University of Copenhagen). To evaluate the effect of synthetic peptides and the recombinant IgI module on aggregation of the high density microwell cultures of primary hippocampal neurons, the number of aggregates in each well was counted 24 h after plating.

To evaluate the length of processes of hippocampal neurons, low density cultures in LabTek coverslides were fixed in 4% w/v paraformaldehyde for 15 min, stained with Coomassie Blue R250 (4 g/liter in 45% v/v ethanol and 45% v/v acetic acid) for 20 min, and recorded 24 h after plating. By means of the ProcessLength software package (Protein Laboratory, University of Copenhagen), an unbiased counting frame containing a grid with a user-defined number of test lines was super-
FIG. 3. Effect of the monomeric form of the P2 peptide (P2m) (○) and the IgII (●) module of NCAM on cell aggregation of dissociated rat hippocampal neurons. The cultures were grown for 24 h. The number of aggregates in the cultures treated with P2m or IgII is expressed as a percentage of the number of aggregates in control cultures. An increasing number of aggregates reflects a decreasing cell-cell adhesion. Four independent experiments were performed. Results are given as mean ± S.E. *, p < 0.05; **, p < 0.01; ***, p < 0.001 (as compared with the number of aggregates in control cultures).

FIG. 4. Confocal micrographs of rat hippocampal neurons grown at a low density in the absence (A) or presence (B–D) of 0.8 μM P2d for 8 h (B), 24 h (A and C), or 96 h (D). The cells were immunostained for GAP-43. Scale bar, 10 μm.
imposed on images of the cell cultures. The number of intersections of cellular processes with the test lines was counted and related to the number of cell bodies, thereby allowing quantification of the total neurite length per cell (19). Between 150 and 250 cells were analyzed in each group in each individual experiment. The average neurite length of control, untreated neurons was 9 μm/cell.

**Immunofluorescence Staining for GAP-43**—Hippocampal cultures were rinsed in sodium phosphate buffer (0.1 M NaH2PO4, 50 mM sucrose, 0.4 mM CaCl2, pH 7.1), fixed in 4% w/v paraformaldehyde in sodium phosphate buffer for 30 min at room temperature, blocked with 10% v/v normal goat serum in 1% w/v bovine serum albumin in phosphate-buffered saline for 1 h, and washed with phosphate-buffered saline containing 1% w/v bovine serum albumin and 0.2% w/v saponin.

Neurons were subsequently incubated with rabbit anti-rat GAP-43 polyclonal antibodies diluted 1:1000 for 2 h at room temperature. Bound antibodies were detected with fluorescein-conjugated goat anti-rabbit IgG diluted 1:100 (Molecular Probes, Eugene, OR). Slides were mounted using Prolong Antifade (Molecular Probes) and scanned with a MultiProbe 2010 laser scanning confocal microscope equipped with an argon/krypton laser (Molecular Dynamics, Sunnyvale, CA) and an oil immersion ×60 objective, 1.4 NA (Nikon, Tokyo, Japan).

**ERK1/2 Phosphorylation Assay**—Hippocampal neurons were seeded in 60-mm tissue culture dishes and grown for 6 h in Neurobasal medium. Cells were treated with peptides for 15, 30, and 60 min. Cell extracts were prepared as described previously (15). Cell lysates were separated by SDS-PAGE and transferred to a polyvinylidene fluoride membrane (Millipore, Bedford, MA). The membrane was blocked for 1 h at room temperature in Tris-buffered saline (TBS) containing 0.05% v/v Tween 20 and 5% w/v non-fat dry milk and incubated overnight with PhosphoPlus p42/44 MAP kinase (Thr202/Tyr204) antibody (New England Biolabs, Beverly, MA) diluted 1:1000 in TBS. After washing in TBS, the membrane was incubated for 1 h at room temperature with a goat anti-rabbit IgG horseradish peroxidase conjugate diluted 1:2000 in TBS containing 5% w/v non-fat dry milk. The membrane was washed again in TBS, and bound secondary antibodies were visualized by enhanced chemiluminescence (ECL) (Amersham Biosciences). To estimate the total amounts of ERK1 and ERK2, the membrane was stripped with 50 mM dithiothreitol, 2% SDS in 62.5 mM Tris-HCl, pH 6.8, for 30 min at 60 °C and reprobed with anti-MAP kinase (p42/p44 MAP kinase (Thr202/Tyr204) antibody kit from New England Biolabs). The exposed x-ray films were scanned and quantified using the PrAverB image analysis software (Protein Laboratory, University of Copenhagen).

**Statistics and Graphical Presentations**—Statistics and graphical presentations were carried out using the Fig-P version 2.2 software package (Biosoft, Cambridge, UK). Statistical evaluations were performed using a two-sided Student’s t test. Unless stated otherwise, the results are given as mean ± S.E.
RESULTS

The P2 peptide Binds to the First Ig Module of NCAM—We synthesized a peptide, termed P2, whose sequence, GRILAR-GEINFK, corresponds to residues Gly172–Lys183 of human, rat, mouse, and chicken NCAM, spanning the C-terminal part of the F β-strand, the F-G β-hairpin turn, and the N-terminal part of the G β-strand of the IgII module (Fig. 1). IgII has been shown to bind to the IgI module of NCAM (8–10, 20). Since the P2 peptide corresponds to the homophilic binding sequence of the IgII module of NCAM, we tested the ability of P2 to bind to the recombinant IgI module by employing surface plasmon resonance analysis. Because it has been shown that the potency of a peptide ligand may be strongly enhanced when the peptide is prepared in a multimeric form (16, 21, 22), the P2 peptide was synthesized as a dendrimer (four peptide mole-

\[ \text{[P2d]/[IgI]} \]

Fig. 7. Inhibition of neurite outgrowth from hippocampal neurons induced by P2d after preincubation of the peptide (0.8 μM) with the IgI module of NCAM in different concentrations at 25 °C for 30 min before plating. Cultures were grown for 48 h. Four independent experiments were performed. Results are given as mean ± S.E.* p < 0.05; ** p < 0.01 (as compared with the induction of neurite outgrowth by P2d in the absence of IgI).

\[ [\text{IgII}]/[P2d] \]

Fig. 8. Dependence of the concentration of free P2d peptide in solution ([P2d]_free) on the concentration of the IgI module of NCAM ([IgI]) with the assumption that \( K_a = 4.7 \mu M \) (solid curves) or that \( K_a = 55.0 \mu M \) (dashed curves). \([\text{IgI}]/[P2d] \), the molar ratio of the concentrations of the IgI module and P2d peptide. n, the number of IgI binding sites in the P2d peptide (curves are shown for \( n = 1 \) and \( n = 4 \)).

The IgII module, thereby interfering with homophilic NCAM binding.

P2 Inhibits Aggregation of Hippocampal Neurons—The IgII module of NCAM has been shown to interfere with NCAM-mediated cell adhesion (16). To test whether P2 also could affect cell-cell adhesion, hippocampal neurons were seeded at high density (50,000 cells/well) in microwell dishes allowing formation of large aggregates during 24 h (18). In Fig. 3, it can be seen that treatment with the monomeric form of the P2 peptide (P2m) caused an increase in the number of aggregates in a dose-dependent manner. In P2-treated cultures, aggregates were smaller than those in control cultures, indicating that P2m as well as IgII inhibit intercellular adhesion, although P2m was 10 times less potent than the recombinant IgII module. Thus, the P2 peptide inhibited aggregation of hippocampal neurons, presumably by binding to the first IgI module, thereby interfering with homophilic NCAM binding.

P2 Stimulates Neurite Outgrowth from Single Hippocampal Neurons—Previously, it has been shown that the IgII module of NCAM stimulates neurite outgrowth at a concentration of 1 μM (16). To test whether P2 also could induce neurite outgrowth, hippocampal neurons were grown in serum-free medium at a low density, precluding cell-cell adhesion. In untreated cultures, hippocampal neurons do not differentiate, as reflected by the extension of no or very short processes (Fig. 4A). However, when hippocampal neurons were treated with the dendrimeric form of P2, P2d, sprouting was observed already 8 h after plating (Fig. 4B), and the extension of long neurites took place within the first 24 h (Fig. 4C). After 4 days, outgrowth of multiple branching neuronal processes (neurites) was observed (Fig. 4D). In Fig. 5A, it can be seen that treatment of hippocampal neurons with various concentrations of P2d for 24 h induced a neuritogenic response, the maximal stimulation being ob-

\[ \text{Concentration of [P2d]}_\text{free} \]

\[ [\text{IgI}]/[P2d] \]

n=4
n=1
n=4
n=1
Neuritogenic Activity of a Peptide Sequence from NCAM-IgII

It can be seen that the readdition of P2 after 24 h in all tested concentrations was without effect on neurite outgrowth induced by P2 applied during plating, suggesting that P2, by binding to the IgI module of NCAM, may act as a trigger in the activation of intracellular signaling cascades, leading to neuronal differentiation. When this process has been initiated, no further activation seems to be needed.

Preincubation of P2 with Recombinant IgI of NCAM Inhibits the Neuritogenic Effect of the Peptide—Since P2 binds to the IgI module of NCAM, we tested whether the neuritogenic effect of the peptide could be abrogated by incubation of the peptide with the recombinant IgI module. IgI in itself has no stimulatory effect on neurite outgrowth (16). In Fig. 7, it can be seen that preincubation of P2d with IgI for 30 min before addition to cell culture inhibited the neuritogenic activity of the peptide in a dose-dependent manner. A statistically significant reduction of the neuritogenic effect of P2d was observed at [IgI]/[P2d] ratios of 8/1 and 16/1.

The P2d binding to the recombinant IgI module of NCAM was determined by plasmon surface resonance analysis to have a $K_d$ of $4.7 \pm 0.9 \times 10^{-10}$ M. Presuming that the binding of P2d to IgI is described by simple first-order kinetics, we calculated the concentration of free P2d in solution in the presence of IgI. By definition of the dissociation constant, the concentration of P2d is as shown in Equation 1,

$$[P2d] = K_d \frac{[P2d]_0 [IgI]}{[IgI]_0^2}$$

(Eq. 1)

where $[P2d]$ is the molar concentration of the binding sites of P2d peptide, $[IgI]$ is the molar concentration of the IgI module, and $[P2d][IgI]$ is the molar concentration of the P2d-IgI complex.

Defining the concentration of P2d and IgI at $t = 0$ as $[P2d]_0$ and $[IgI]_0$, respectively, we obtain $[P2d][IgI] = [P2d]_0 - [P2d] = [IgI]_0 - [IgI]$. Therefore, as shown in Equation 2,

$$[P2d] = K_d \frac{[P2d]_0 [P2d]_0 - [P2d]}{[IgI]_0^2 - [P2d]}$$

(Eq. 2)

The solutions $S_1$, $S_2$ of this equation are shown in Equations 3 and 4.

$$S_1 = \frac{1}{2} \left(-[IgI]_0 + K_d - [P2d]_0\right)$$

$$S_2 = \left([IgI]_0 + K_d - [P2d]_0\right)^2 + 4K_d[P2d]_0$$

(Eq. 3)
Neuritogenic Activity of a Peptide Sequence from NCAM-IgII

Effects of P2d at various peptide concentrations on phosphorylation of ERK1 and ERK2 in hippocampal neurons. Lysates of control cultures (lane 1), cultures treated with either P2d (lanes 2–4), or scrambled P2d (lanes 5 and 6) at peptide concentrations of 2 μM (lanes 2 and 5) or 4 μM (lanes 3, 4, and 6) for 15 min were submitted to SDS-PAGE and immunoblotted using either polyclonal anti-phosphoMAP kinase antibodies or polyclonal anti-MAP kinase antibodies. In lysate 4, the culture was additionally treated with 40 μM MEK1/2 inhibitor, U0126.

where n is the number of IgI binding sites on a single P2d molecule. Since P2d has four potential binding sites for IgI, the value of n varies from 1 to 4. Provided that $K_d = 4.7 \mu M$, $[IgI]_0 = 0.9 \mu M$, $[P2d]_0 = n \times 0.8 \mu M$, n = 1 or 4, and using Equation 6, we calculated $[P2d]_{free}$ as a function of the $[IgI]/[P2d]$ ratio (Fig. 8). From Fig. 7, it can be seen that IgI inhibited the P2d-induced neurite outgrowth at $[IgI]/[P2d]$ molar ratios of 8/1 and 16/1. From Fig. 8, we find that at $[IgI]/[P2d] = 16/1$, the concentration of free P2d approaches 0.2 μM. This is in a good agreement with the results of the P2d-induced neurite outgrowth (Fig. 5B), which shows statistically significant ($p < 0.001$) reduction in neurite length at a concentration of 0.2 μM of P2d as compared with neurite outgrowth observed when using 0.8 μM P2d. This supports the suggestion that the P2 peptide exerts its neuritogenic effect via binding to the first module of NCAM expressed on the surface of neurons.

Identification of Important Amino Acid Residues of the P2 Sequence by Substitution Analysis—To analyze the contribution of individual amino acid residues to the neuritogenic effect of P2, single amino acid residues in P2m were systematically replaced with alanine residues. In Fig. 9, it is seen that none of the single amino acid substitutions resulted in a statistically significant reduction of the neuritogenic effect of P2m. Interestingly, substitutions of Arg2 or Ile3 with alanine each resulted in a statistically significant increase of the neuritogenic activity of P2m. Double substitutions of Arg2 →Arg6, Arg2 →Ile6, Arg2 →Ile6, Ile3 →Ile6, Arg2 →Asn6, or Gly2 →Asn6 all resulted in a reduction of the neuritogenic effect of P2m. These data indicate that the presence of at least one arginine (Arg2 or Arg6), at least one isoleucine (Ile3 or Ile6), and Asn6 is important for the neuritogenic effect of P2. When the P2 sequence was truncated from the N terminus, the deletion of one amino acid (glycine) was tolerated, but further deletion of Arg6 abolished the neuritogenic effect. The deletion of the C-terminal Phe11–Lys12 also abolished the neuritogenic effects (the peptide in which only Lys12 was removed was not soluble). Single substitution of Phe11 or Lys12 with alanine had no effect, indicating that both the length of the peptide and the presence of the basic amino acid residues at the N and C termini are important for the neuritogenic activity of P2.

Treatment of Hippocampal Neurons with P2 Activates the MAPK Kinases ERK1 and ERK2—Previously, NCAM-dependent neurite outgrowth has been demonstrated to be accompanied by an activation of the Ras-MAP kinase signaling pathway (14, 15, 23). We therefore tested whether the neuritogenic response to P2 requires the activation of the ERK1 and ERK2. Hippocampal neurons were treated with U0126, an inhibitor of MEK1 and MEK2, which can activate ERK1 and ERK2. In Fig. 10, it can be seen that treatment with U0126 inhibited P2-induced neurite outgrowth in a dose-dependent manner.

We have recently demonstrated that another ligand of NCAM identified by combinatorial chemistry, the C3 peptide, which similarly to P2 mimics NCAM function (although less...
efficiently (16), induces phosphorylation of ERK1 and ERK2 in PC12-E2 cells (15). Therefore, we compared the effects of P2d and C3d on phosphorylation of the terminal kinases ERK1 and ERK2 in cultures of hippocampal neurons. In Fig. 11, A–C, it can be seen that treatment of hippocampal neurons with P2d resulted in a strong phosphorylation of ERK1 and ERK2 peaking around 15–30 min and decreasing 60 min after stimulation, whereas the C3d-induced phosphorylation of ERK1 and ERK2 reached its maximum at 60 min (and remained at the maximal level for at least 6 h, data not shown). Activation of ERK1 and ERK2 by P2d was dose-dependent. In Fig. 12, it can be seen that treatment of hippocampal neurons with 4 μM P2d for 15 min resulted in a stronger increase in kinase phosphorylation than treatment with 2 μM P2d. An inhibitor of MEK1 and MEK2, UO126, completely blocked P2d-induced phosphorylation of ERK1 and ERK2. In contrast, treatment of cultures with various concentrations of the control peptide, scrP2d, did not affect phosphorylation of ERK1 and ERK2. We conclude that the neuritogenic response induced by P2, similarly to that induced by physiological homophilic NCAM interactions, requires the activation of the MAP kinases.

DISCUSSION

In this study, we demonstrate that a peptide, GRILAR-GEINFK, termed P2, which corresponds to the sequence Gly172–Lys183 of NCAM, inhibits aggregation and stimulates neurite outgrowth of hippocampal neurons. We show that P2 binds to the first Ig module of NCAM and suggest that P2 mimics physiological homophilic NCAM binding. Several observations support this suggestion.

First, the sequence of the second Ig module of NCAM corresponding to P2 contains the residues, Arg173, Arg177, and Glu179, which were identified by NMR as being involved in the homophilic binding between IgI and IgII. Site-directed mutagenesis corroborated these results (9). The x-ray structure of the IgI-IgII dimer revealed that Arg173, Leu175, and Ile180 of the P2 sequence constitute a part of a hydrophobic pocket for the side chains of residues Phe19, Tyr25, and Gly178. Moreover, P2d forms hydrogen bonds with the amino group in the side chain of Lys18 and the amino group of Phe13 of IgII (10). However, the neuritogenic effect is 7–15 times larger for the denudimeric form of P2 (Figs. 5 and 7) than that reported for the dendraforma of C3 (16). The observed differences may result in varying degrees of clustering of NCAM on the surface of the hippocampal neurons upon binding of different peptide ligands to IgI, thereby resulting in differences in the kinetics of activation of the Ras-MAP kinase pathway (Fig. 11) and subsequently in the magnitude of the neuritogenic response.

In conclusion, we have identified a new potent peptide ligand of NCAM, P2, which corresponds to a 12-amino acid sequence in the second NCAM Ig module, binds to the first Ig module, and mimics homophilic NCAM binding with respect to modulation of cell-cell adhesion and induction of neuronal differentiation. As a potent mimetic of NCAM, P2 may prove useful as a lead in the development of therapies for neurodegenerative disorders.

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Induction of Neuronal Differentiation by a Peptide Corresponding to the Homophilic Binding Site of the Second Ig Module of the Neural Cell Adhesion Molecule

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