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The Role of Glycoproteins in Neural Development, Function, and Disease

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Abstract

Glycoproteins play key roles in the development, structuring, and subsequent functioning of the nervous system. However, the complex glycosylation process is a critical component in the biosynthesis of CNS glycoproteins that may be susceptible to the actions of toxicological agents or may be altered by genetic defects. This review will provide an outline of the complexity of this glycosylation process and of some of the key neural glycoproteins that play particular roles in neural development and in synaptic plasticity in the mature CNS. Finally, the potential of glycoproteins as targets for CNS disorders will be discussed.

Index Entries: Glycoproteins; cell-adhesion molecules; teratogenic neurotoxins.

Introduction

Glycoproteins play a pivotal role in the structuring and functioning of the CNS and exist primarily as secreted or membrane-bound proteins. Neural cells express a great structural variety of terminal saccharides, with sialylation (especially α2,3 linked sialic acid) and α1,3 fucosylation of the nonreducing terminal GlcNAc residue being particularly enriched (Finne, 1990). Up to 85–90% of glycoprotein carbohydrates are attached by *N*-glycosidic linkages to the protein backbone, with the remainder being O-linked (Margolis and Margolis, 1989). In particular, complex oligosaccharides are seen to be dominant with most containing tri- and tetra-antennary structures (*see* Monosaccharide Chain of O-Linked Glycoproteins).

The functions of neural cell glycoproteins are extremely varied. During development, they play a critical role in the modulation of

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growth-cone formation (Gordon-Weeks and Williamson, 1992). In the mature nervous system, they are involved in the process of neurotransmitter release from synaptic vesicles (Luithi et al., 1991) and furthermore, many neural receptors, such as G protein-coupled receptors, acetylcholine receptors, sodium channels, and opiate receptors, are glycoproteins (Wing, 1994). Glycoproteins, however, play a particular role in the modulation of cell–cell and cell–matrix interactions within the CNS, with the best characterized of these being the neural cell-adhesion molecule (NCAM) (Rutishauser and Landmesser, 1996; Baldwin et al., 1996). Other key neural glycoproteins that have been demonstrated to play a role in the mediation of neural cell adhesion include the amyloid β precursor protein (AβPP), N-cadherin, L1, Thy-1, the myelin-associated glycoprotein (MAG), the integrin proteins and the components of the extracellular matrix (Martini, 1994; Small et al., 1996; Schachner and Martini, 1995).

Many neural cell glycoproteins express a functional carbohydrate epitope whose expression may be regulated independently of the core protein and these serve to "fine tune" the functions of the protein backbone (Wing, 1994; Schachner and Martini, 1995). These oligosaccharide groups may be either N-linked or O-linked glycans, although the O-linked carbohydrate ligands are generally displayed as smaller oligosaccharides than those of the N-linked groups. Key N-linked oligosaccharides that have been characterized include L2/HNK-1 (Schachter and Martini, 1995), polysialic acid (Rutishauser and Landmesser, 1996), Le^x/CD15/SSEA-1 (Streit et al., 1996), and oligomannosidic glycans (Schmitz et al., 1995). The presence of O-linked glycans can cause the conformation of the peptide core to become stiff and extended, often presenting as a clustered O-linked glycosylation domain (Jentoft, 1990). This high level of local clustering of the carbohydrate ligands may be important for recognition events such as the dynamic cell–cell and cell–extracellular matrix interactions.

Protein Glycosylation

There are three major classes of glycosylated macromolecules that are associated with membrane systems: glycolipids, glycoproteins, and glycosaminoglycans (Stoddart, 1979).

Glycoproteins form a diverse group of complex macromolecules that are probably best defined as conjugated proteins containing one or more heterosaccharides, covalently bound to the polypeptide chain, as their prosthetic group (Bahl, 1992). Glycosylation can be considered as one of the most common covalent modifications undergone by newly synthesized proteins (Lis and Sharon, 1993). It is also by far the most diverse, both with respect to the kind of amino acids that are modified and the structures attached (Parekh, 1994). This diversity has both chemical and biological origins. The diversity caused by the former lie in the ability of monosaccharides to combine with each other in a number of ways that differ in both sequence and chain length. The additional covalent attachment of sulphate, phosphate, acetyl, or methyl groups to the sugars provides a further structural diversification. Hence, in theory, an enormous variety of glycans, both oligosaccharides and polysaccharides, can be generated from a relatively limited number of monosaccharides. Whereas proteins are primary gene products, glycans are secondary, and this gives rise to biological diversity. As a result, glycosylation is both species and cell specific and is further influenced by additional factors that may modulate either the structure of the protein backbone or the carbohydrate attachment site.

Multiple carbohydrate units are often present on an individual glycoprotein that are attached directly to the protein at different positions by either an N-linkage (to Asn), an O-linkage to Ser/Thr, or alternatively as a component of the glycosylphospatidylinositol (GPI) membrane anchor (Lis and Sharon, 1993). Hence the glycosylation sites present can be substituted with glycan structures, ignored, or variably occupied and it is this ambiguity that leads to macroheterogeneity. The more subtle changes in the individual carbohydrate residues within a gly-

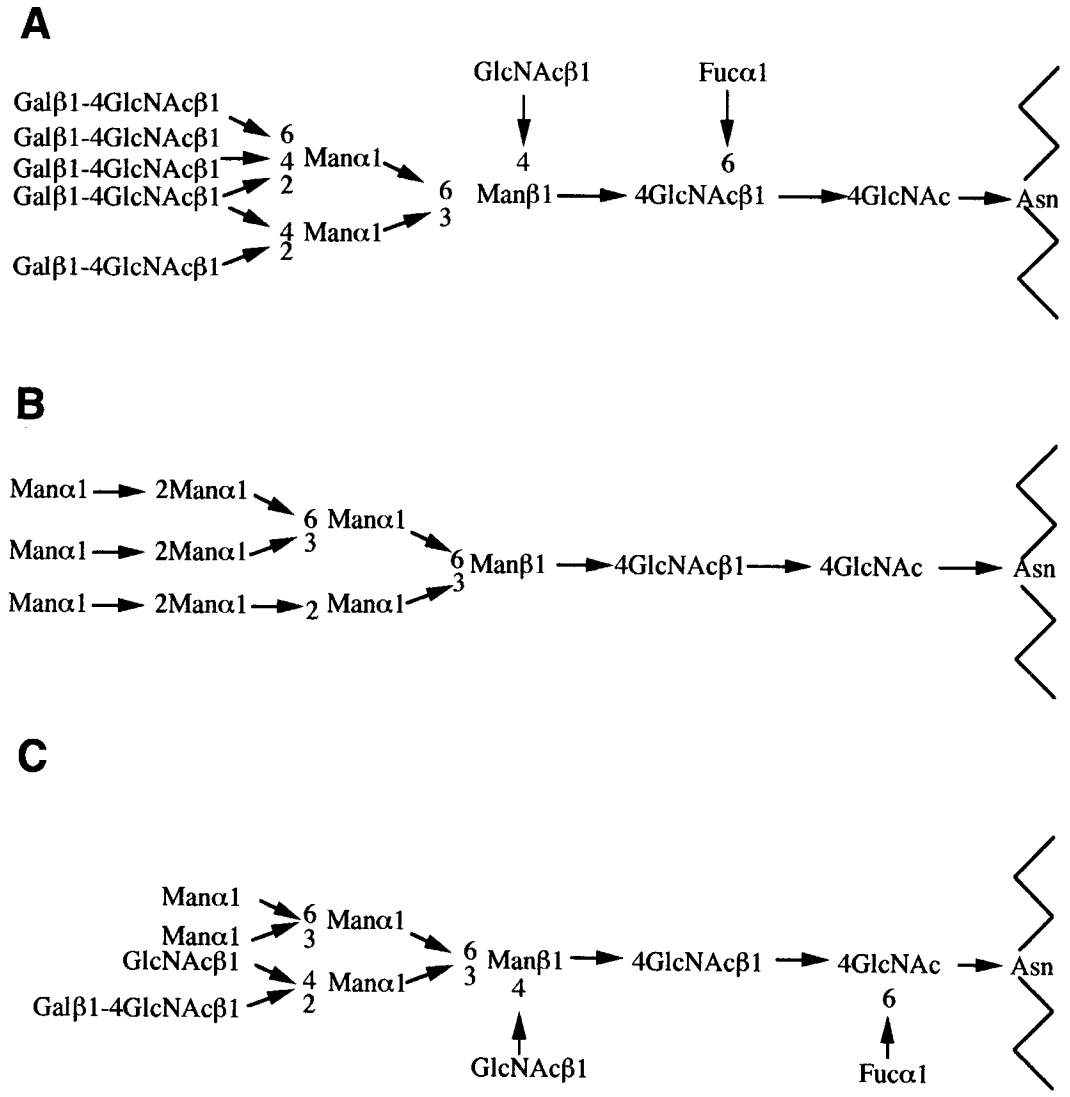

Fig. 1. Diagrammatic structure of (**A**) complex, (**B**) high-mannose, and (**C**) hybrid N-linked oligosaccharides. Asn = asparagine, GlcNAc = *N*-acetylglucosamine, Man = mannose, gal = galactose.

can structure are termed the microheterogeneity and it is this microheterogeneity that creates discrete subsets, or glycoforms, of a glycoprotein with different physical and biochemical properties, which in turn may lead to functional diversity (Jenkins et al., 1996).

N-Linked Glycoproteins

The N-linked carbohydrates fall into three main categories, all of which share a common pentasaccharide 'trimannosyl' core structure (Fig. 1). According to the structures and the location of the extra sugar residues added to the trimannosyl core, the N-linked sugar chains are classified as complex, high mannose, and hybrid-type structures (Kobata, 1992).

Complex N-Linked Glycoproteins

The complex-type structures contain no mannose residues outside the tri-mannosyl

core but rather 2–4 lactosamine or sialyllactosamine units linked to the α-linked mannose (Man) residues of the core forming bi-, tri-, tetra-, and penta-antennary structures (Fig. 1A). In the developing brain tissue, polysialosyllactosamine units, such as those attached to NCAM, constitute a major proportion of the outer chains.

High Mannose N-Linked Glycoproteins

The high-mannose-type oligosaccharides contain only a mannosyl residues in addition to the tri-mannosyl core (Fig. 1B). Variation is formed in these sugar chains by the numbers and the locations of up to four Man α1,2 residues linked to the three nonreducing terminal-mannosyl residues of the common heptasaccharide.

Hybrid N-Linked Glycoproteins

The hybrid oligosaccharides combine certain structural features of both the high mannose and the complex types (Fig. 1C). One or two α-mannosyl residues are linked to the Man α1,6 arm of the tri-mannosyl core as in the case of the high-Man type, and the outer chains found in complex-type sugar chains are linked to the Man α1,3 arm of the core of this group. The presence or absence of the α-fucosyl residue and the bisecting GlcNAc linked to the tri-mannosyl core also produce structural variations in the sugar chains of this subgroup.

N-Linked Biosynthesis

N-linked sugar chains are formed by a series of complex pathways that are separated both spatially and temporally into discrete enzymatic steps, generally categorized as early-, middle- and late-stage processing. These stages involve the endoplasmic recticulum (ER), different stacks of the Golgi apparatus, and the trans-Golgi network (TGN) (Kornfield and Kornfield, 1985).

The first stage in the biosynthetic pathway is the transfer of *N*-acetyl glucosamine (GlcNAc) from UDP-GlcNAc to a polyisoprenol monophosphate dolichol phosphate (Dol-P). This is followed by the transfer of a second GlcNAc and five mannose residues (Kobata, 1992) and the lipid-bound heptasaccharide is finally converted to $(Glc)_3$-$(Man)_9$-$(GlcNAc)_2$-P-P-Dol by the subsequent addition of four α-mannosyl residues from Dol-P-Man and three α-glucosyl (Glc) residues from Dol-P-Glc. The tetradecasaccharide of the lipid derivative is then transferred *en bloc* to the asparagine (Asn) residue of the polypeptide chain by the catalytic action of a dolicholdiphosphoryl oligosaccharide: polypeptide oligosaccharyltransferase, which resides in the membrane of the endoplasmic reticulum. Studies have shown that only Asn residues in the sequence of Asn-Xaa-Ser/Thr can be glycosylated (where Xaa can be any one of the twenty natural amino acids, except perhaps aspartic acid or proline; Ronin et al., 1981).

The polypeptide containing the tetradecasaccharide is then transported to the Golgi apparatus and as it passes through the endoplasmic reticulum (Fig. 2), three α-glucosyl residues and at least one α1,2 Man residue are removed by the action of two α-glucosidases and an α-mannosidase that reside within the membrane of this organelle. A limited trimming of the mannosyl residues then occurs in the synthesis of glycoproteins of the high-Man type. However, if an intermediate is destined to become a glycoprotein of the complex type, four α1,2 mannosyl residues are released resulting in a $(Man)_5$ $(GlcNAc)_2$ species (Tulsiani et al., 1982; Fig. 2).

The glycoprotein is translocated to the medial Golgi, where the core mannose residues are trimmed by the enzymes mannosidase I and II prior to the subsequent addition of further GlcNAc residues by GlcNAc-transferase (GnT). It is at this stage of the biosynthetic process that it is determined whether the oligosaccharide will be of the high-mannose, complex, or hybrid type (Fig. 1) and there is a complex interaction between the actions of the mannosidase and GnT enzymes (Dunphy et al., 1985). There are at least 5 GnT enzymes, each with a different substrate specificity and these can transfer GlcNAc residues in a specific order to result in a diverse number of

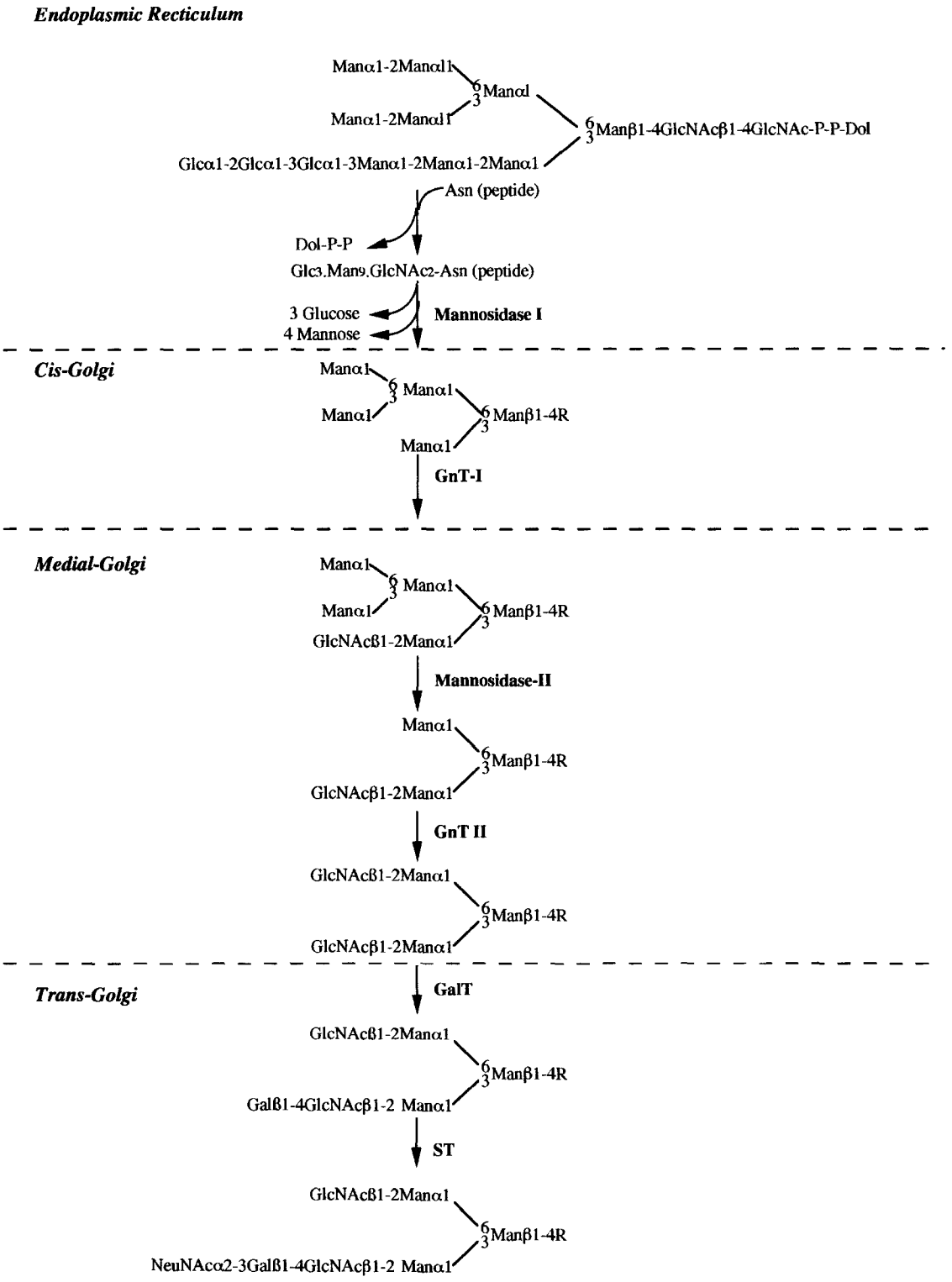

Fig. 2. Diagrammatic representation of the N-linked oligosaccharide biosynthetic pathway outlining the extension of one arm of a complex sugar chain. GnT = *N*-acetylglucosaminyltransferase; GalT = galactosyltransferase; ST = sialyltransferase.

oligosaccharide structures (van den Eijnden and Joziasse, 1993). The penultimate step in the processing of N-linked oligosaccharides is the transfer of a galactose (Gal) residue in β1,4 linkage to the GlcNAc residue, a reaction catalyzed by galactosyltransferase. This then provides a substrate for the transfer of the terminal sugar residue.

The terminal sugar group present on a large number of N-linked oligosaccharides, as well as other glycoconjugates such as the gangliosides, is usually sialic acid which is a family of 9-carbon carboxylated sugars. The most common is *N*-acetylneuraminic acid (2-keto-5-acetamido-3,5-dideoxy-D-glycero-D-galacto-nonulopyranos-1-onic acid; NeuNAc), (Schauer, 1982). Sialic acid has been particularly associated with the modulation of cell adhesion because of the negative charge properties associated with the ionized carboxyl group that sialic acid bears at the C2 position.

The transfer of sialic acid, in the form of the activated sugar (CMP-NeuNAc) is catalyzed by the sialyltransferase (ST) family of glycosyltransferase enzymes. At least 19 ST isozymes are required to synthesise all of the known sialyloligosaccharide sequences, each being enzymatically distinguished by its specificity for the sequence of the acceptor oligosaccharide and the linkage formed between the sialic acid and the sugar to which it is attached (Harduin-Lepers et al., 1995; Sasaki, 1996). Because of its charge, NeuNAc is considered to be one of the most important constituents of the carbohydrate moiety of many glycoconjugates and therefore the activities of the controlling enzymes are vital in the determination of cellular glycosylation potential. Whereas ST is preferentially located in the trans Golgi and the trans-Golgi network (TGN), enzyme activity has also been reported at the level of the synaptosomal membrane where it may play a role in the local control of glycosylation of cell-surface components (Breen and Regan, 1986). A soluble form of the enzyme has also been reported that may serve to act as a marker of tissue ST activity (Maguire and Breen, 1995; Maguire et al., 1994).

The cellular glycosylation sequences are presumed to reflect the expression of the corresponding GTs, with strong support for this idea coming from transfection studies and the use of expression vectors to alter the glycosylation machinery (Paulson et al., 1989; Breen et al., 1997).

For the generation of N-linked glycoproteins, there are three primary ST enzyme groups: α2,3ST, α2,6ST, and α2,8ST (PST and STX) with the latter controlling the biosynthesis of the polysialic acid (PSA) epitope (Fig. 3) (*see* Polysialic Acid). Each of the ST enzymes contains a common 46-amino acid sialylmotif sequence (located in the catalytic domains of the enzyme), which is believed to contain a CMP-NeuNAc-binding site (Datla and Paulson, 1995) and which has proven to be an extremely useful tool for the cloning of ST cDNAs. The constituent ST enzymes differ either in their substrate specificities or in the nature of the glycosidic linkages that they form between sialic acid and the carbohydrate acceptor (Harduin-Lepers et al., 1995).

The β-galactoside α2,6 ST, which terminates sugar chains of glycoproteins with NeuNAcα2,6Galβ1,4GlcNAc linkages was the first to be cloned and demonstrates a strikingly differential expression in rat tissues (Weinstein et al., 1987; Wen et al., 1992), with the level of enzyme activity being found to be highest in the liver, with a 10–100-fold lower activity in tissues such as ovary, brain, and heart (Paulson et al., 1989). α2,6ST is a glycoprotein that contains at least two N-linked carbohydrate chains, a large proportion of which are believed to be of the noncomplex type (Fig. 1) and are thus endoneuraminidase-H resistant (Colley et al., 1992). The carbohydrate chains of the enyme may, however, be important in regulating the catalytic activity of the enzyme and treatment of the enzyme with endoneuraminidase in vitro results in a decrease in catalytic activity (Fast et al., 1993). Other cellular mechansims also exist for the control of α2,6 ST activity. The enzyme can exist as an inactive dimer, generated by a disulfide bond (Ma and Colleg, 1996) and two forms of the enzyme that

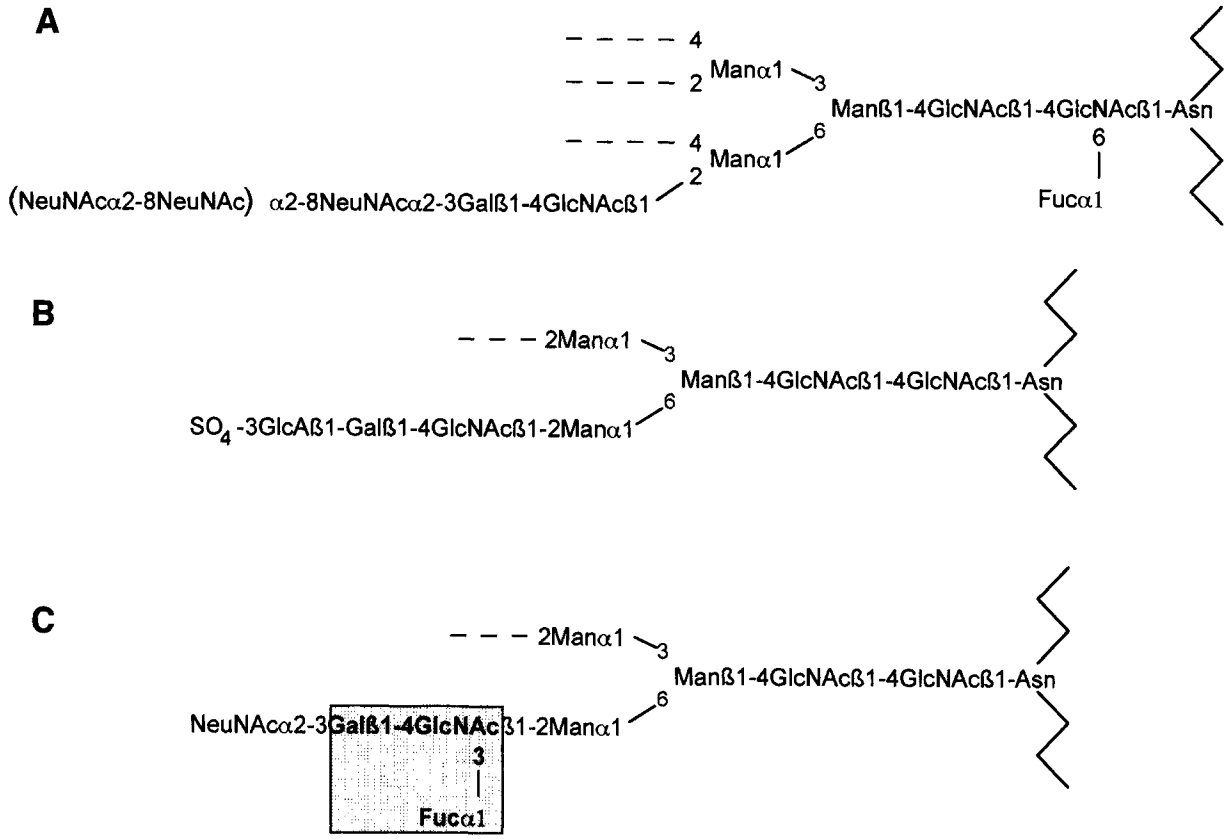

Fig. 3. The proposed structure of (**A**) polysialic acid, (**B**) the L2/HNK-1 epitope, and (**C**) CD15/Lex (outlined in the shaded area).

differ by one amino acid but, have very different properties, have been reported in the liver (Ma et al., 1997).

Several N-linked glycoproteins contain both α2,3 and α2,6-linked terminal sialic acid residues in a specific sialylation pattern and there is a suggestion that there may a competition for the transfer of penultimate residues by the 2 primary ST enzymes, with the ratio of linkages formed by each reflecting the relative enzyme activities within the cell. This has been illustrated by the overexpression of α2,6ST cDNA in *Xenopus* oocytes (Livingston et al., 1990) or in mammalian cells (Breen et al., 1998) resulting in a decrease in α2,3-linked sialic acid. As an α2,3-linked sialic acid residue is a prerequisite for PSA generation, this competition between the α2,3 and α2,6 ST may play a role in the regulation of PSA expression. However, a recent study has suggested that the two ST enzymes may also demonstrate a preference for both the acceptor glycan chain and for the specific glycoprotein backbone. Using desialylated glycoproteins as acceptors, α2,3ST preferentially sialylated complex *N*-glycans over diantennary *N*-glycans. Furthermore, the α2,3ST showed a much greater preference for intact glycoproteins over glycopeptides than did α2,6ST. These results demonstrate that whereas the two enzymes may sialylate the same substrate, they are capable of demonstrating a preference for both the glycan and the glycoprotein backbone.

Several factors have been demonstrated to preferentially stimulate the expression of the individual ST enzymes. Whereas early studies

reported that expression of the α2,6ST enzyme could be stimulated by the synthetic glucocorticoid, dexamethasone, in hepatic cells (Wang et al., 1989), more recent studies have suggested that the CNS expression of the enzyme is similarly controlled. Dexamethasone, however, has no effect on the activity of α2,3ST (Coughlan et al., 1996) although other agents, such as chronic low-level lead, have been demonstrated to stimulate the α2,3ST enzyme with no effect on the α2,6ST (Hayes and Breen, unpublished results).

The generation of the PSA chain (Fig. 3), expressed primarily on NCAM (*see* NCAM), is controlled by two polysialosyltransferase enzymes—PST and STX (Yoshida et al., 1995; Kojima et al., 1995; Eckhardt et al., 1995; Angata et al., 1997) and the expression of these enzymes corresponds well with tissue PSA expression (Nakayama et al., 1995; Scheiddegger et al., 1995) with both exhibiting similar developmental patterns (Oka et al., 1995). Both enzymes are capable of catalyzing the addition of the initial sialic acid residue to the α2,3-linked sialic acid residue as well as the subsequent elongation of the α2,8-linked PSA chain (Nakayama and Fukuda, 1996). However, the expression patterns of the two enzymes are significantly different, suggesting distinct roles for the two enzymes within the nervous system. PST is constitutively expressed in most tissues and is not developmentally regulated, whereas STX is expressed primarily in embryonic tissues (Angata et al., 1997). The genomic structure and promoter regions of the mouse STX have been characterized, revealing a TATA-less GC-rich minimal promoter region that probably controls the cell-type specific and developmental expression of the gene (Yoshida et al., 1996).

O-Linked Glycoproteins

In contrast to N-linked sugar chains, O-linked sugar chains have fewer structural rules (Schachter and Brockhausen, 1992). According to the oligosaccharide chain attached, the Ser-(Thr)-O-GalNAc-linked glycoproteins can be categorized into three main classes: monosaccharides, disaccharides, and chains containing more than two residues (Schachter and Brockhausen, 1992).

Monosaccharide Chain of O-Linked Glycoproteins

The simplest oligosaccharide is a single GalNAc residue attached to a Ser/Thr residue. More recently, O-linked GlcNAc residues have also been described in nuclear and cytoskletal proteins and which may play a role in the regulation of protein phosphorylation (Hart et al., 1996).

Disaccharide Chain of O-Linked Glycoproteins

Four types of Ser(Thr)-GalNAc disaccharide chains have been described to date:

1. NeuNAcα2,6GalNAc—Ser(Thr)-R
2. Galβ1,3GalNAc—Ser(Thr)-R
3. GlcNAcβ1,3GalNAc—Ser(Thr)-R
4. GalNAcα1,3GalNAc—Ser(Thr)-R.

More than Two Residue O-Linked Glycoproteins

This class varies in size from trisaccharides, to chains with 18 or more residues. The larger chains contain three distinct regions: a core, a backbone, and a nonreducing terminus. The core consists of a GlcNAc/Gal-GalNAc-Ser/Thr disaccharide group with the potential for different linkages between the sugars. There are at least six core classes that have been described to-date. The backbone of the Ser(Thr)-GalNAc oligosaccharide is then formed by the elongation of the core, which usually involves addition of Gal and N-GlcNAc residues in β-linkages (Schachter and Brockhausen, 1992): The larger Ser(Thr)GalNAc oligosaccharides are frequently terminated by α-linked sugars including fucose and sialic acid and in addition, sulfate groups may be added onto terminal or internal sugars.

Cell-Adhesion Molecules

There are three main classes of neural membrane-associated glycoproteins that modulate

cell–cell adhesion: the integrins, the cadherins, and the immunoglobulin (Ig)-superfamily. However, other cell-surface glycoconjugates, including the amyloid β precursor protein, may also play key roles in this process. In addition, key oligosaccharide groups including PSA, L2/HNK-1, CD15/Le^x (Fig. 3), and oligomannoside groups (Fig. 1) have been demonstrated to modulate cell–cell interaction.

Integrins

The integrin receptors are developmentally regulated heterodimeric glycoproteins, composed of α and β subunits, which have multiple functions within the nervous system. Their ligands include elements of the extracellular matrix (ECM) (Calof et al., 1994), a *cis*-interaction with cell-surface molecules (Felsenfeld et al., 1994; Montgomery et al., 1996), and soluble factors (Einheber et al., 1993; Kadmon and Altevogt, 1997). The specificity of integrin binding to the individual elements of the ECM is dependent on the dimeric structure of the protein (Zutter and Santoro, 1990; Tomaselli et al., 1993) and may be associated with a signaling event following the reorganization of cytoskeletal components at the adhesive sites (Gomez et al., 1996). The integrins play a pivotal role in the events associated with nervous system development and protein mutations or an upset in their temporal expression pattern may result in serious malformations and ultimately be lethal (Yang et al., 1993).

Glycosylation has been demonstrated to be important in integrin function (Veiga et al., 1995; Nakagawa et al., 1996) and certain integrins, for example, have been demonstrated to express the L2/HNK-1 carbohydrate adhesion epitope (Fig. 3B; Pesheva et al., 1987; Smalheiser and Kim, 1995), which may partially mediate the interaction of the β1 integrin with elements of a laminin substrate (Hall et al., 1997, 1993, 1995). In addition, proteoglycans may also play a role in integrin-mediated adhesion as heparin inhibits integrin binding to thrombospondin (Neugebauer et al., 1991). The interactions of integrins with elements of the ECM can be inhibited by the RGD (Arg-Gly-Asp) tripeptide of a number of snake toxins including the disintegrins kistrin, elegantin and albolabrin and the neurotoxin homolog dendrasporin (Lu et al., 1994; Rahman et al., 1995), suggesting that this amino acid sequence may play a key role in integrin function.

Cadherins

N-cadherin is a member of the cadherin multigene family (Redies and Takeichi, 1996) that mediates spatiotemporally regulated cell–cell interactions, both within the nervous system and in other tissues via a Ca^{2+}-dependent homophilic mechanism (Takeichi, 1991; Doherty et al., 1991). The cadherins express complex N-linked carbohydrate side chains (Shore and Nelson, 1991) and *N*-cadherin has also been reported to contain a terminal *N*-GNAc residue linked to an oligosaccharideal chain via a phosphodiester bond. This can be accounted for by the close interaction between the protein and a cell-surface *N*-acetylgalactosaminyltransferase that transfers *N*-acetylgalactosaminephosphate groups to endogenous acceptors Balsamo and Lilien, 1990) and may play a role in the adhesive functioning of the protein (Balsamo et al., 1995).

The intracellular domain of the protein is crucial for its adhesive functioning, suggesting that the cadherins may interact with the cellular cytoskeleton. Furthermore, the associated adhesion-mediated cadherin stimulation of axonal growth occurs via an erbstatin-sensitive tyrosine kinase-phospholipase C gamma cascade (Williams et al., 1994a, b), possibly by the activation of the fibroblast growth factor receptor (Williams et al., 1994c), with the subsequent activation of L- and N-type calcium channels (Volberg et al., 1992; Doherty and Walsh, 1996). This pathway is also shared with NCAM and L1. Treatment with either calcium channel blockers or a Ca^{2+}/calmodulin-dependent kinase inhibitor serves to inhibit the N-cadherin-simulated neurite growth, thus providing an insight into the downstream events following the activation of the cadherin-signaling path-

way (Harper et al., 1994; Williams et al., 1995). Other signaling pathways, including a *cis*-interaction with *N*-acetylgalactosaminylphosphotransferase, may alter the interaction of cadherin with the cytoskeleton and thus inhibits adhesion (Balsamo et al., 1995; Gaya Gonzalez et al., 1991). The extracellular domain of the protein is thought to bind calcium, which serves to stabilize the protein structure, and a tripeptide sequence (His-Ala-Val) is critical in cadherin homophilic interactions (Takeichi, 1991). Other members of the cadherin family that play a role in the mediation of neural cell adhesion include T-cadherin (Fredette and Ranscht, 1994), R- and E-cadherins (Matsunami and Takeichi, 1995; Arndt and Redies, 1996), PB-cadherin (Sugimoto et al., 1996), OB-cadherin (Kimura et al., 1996), and M-cadherin (Bahjaoui Bouhaddi et al., 1997).

Immunoglobulin Superfamily

The third major class of membrane-associated cell adhesion molecules is the Ig-superfamily, the members of which contain at least one extracellular Ig-like domain. These Ig domains are consecutive regions of approx 100 amino acids that are generally disulfide bonded (Williams, 1987). Certain members of the group also contain sequences of approx 90 amino acids that are repeated in the extracellular domain of fibronectin and are termed fibronectin type III repeats. The Ig group includes NCAM, L1/NgCAM/NILE, axonin-1/Tag-1, neurofascin, Nr-CAM/Bravo, thy-1, P_o, and MAG (Fig. 4).

NCAM

NCAM is a cell-surface glycoprotein that is found predominantly on embryonic neuronal, glial, and muscle cell surface, as well as a variety of adult tissues (Edelman, 1988). NCAM was one of the first cell-adhesion molecules to be identified (Rutishauser et al., 1976; Bock et al., 1975; Hirn et al., 1981) and characterized (Thiery et al., 1977), and is involved in both homotypic (neuron–neuron; muscle–muscle) (Thiery et al., 1977) and heterotypic (neuron–glia; neuron–muscle; Keihauer et al., 1985; Drazba and Lemmon, 1990) cellular interactions. Through its mediation of adhesion, NCAM has also been proposed to play a role in promoting neurite outgrowth (Doherty et al., 1990), axonal guidance (Silver and Rutishauser, 1984), and in the formation of neuromuscular synapses (Bixby and Reichardt, 1985).

There are three primary developmentally regulated NCAM isoforms expressed in the nervous system that are formed by alternative splicing of the NCAM gene (Reyes et al., 1991). The three isoforms have molecular weights of approx 180, 140, and 120 kDa (Cunningham et al., 1987) and are termed $NCAM_{180}$, $NCAM_{140}$, and $NCAM_{120}$, respectively (Fig. 4). A secreted form of the protein has also been identified (Gower et al., 1988; Krog et al., 1992). The two higher-molecular-weight isoforms are transmembrane proteins that differ in the length of their cytoplasmic domain, whereas $NCAM_{120}$ is attached to the plasma membrane via a glycosylphosphatidylinositol anchor (He et al., 1986). The expression of the constituent NCAM isoforms is developmentally regulated with the shorter transmembrane form ($NCAM_{140}$), which particularly stimulates adhesion-dependent neurite outgrowth (Doherty et al., 1992; Soffell et al., 1995), being expressed primarily coincident with neural development and the 180 kDa isoform being expressed following synaptogenesis (Pollerberg et al., 1985). The larger cytoplasmic domain of this isoform may serve to stabilize synaptic structures through an interaction with elements of the cytoskeleton (Pollerberg et al., 1987). However, the $NCAM_{180}$-cytoskeletal interaction can be disrupted by calcium-induced proteolysis following the activation of a μ-type calpain that suggests that interaction is susceptible to physiological events that act to increase intracellular calcium levels (Covalt et al., 1991). This may be of particular importance in the plastic processes associated with synaptic reorganization underlying memory and learning (*see* The Role of Glycoproteins in Synaptic Plasticity).

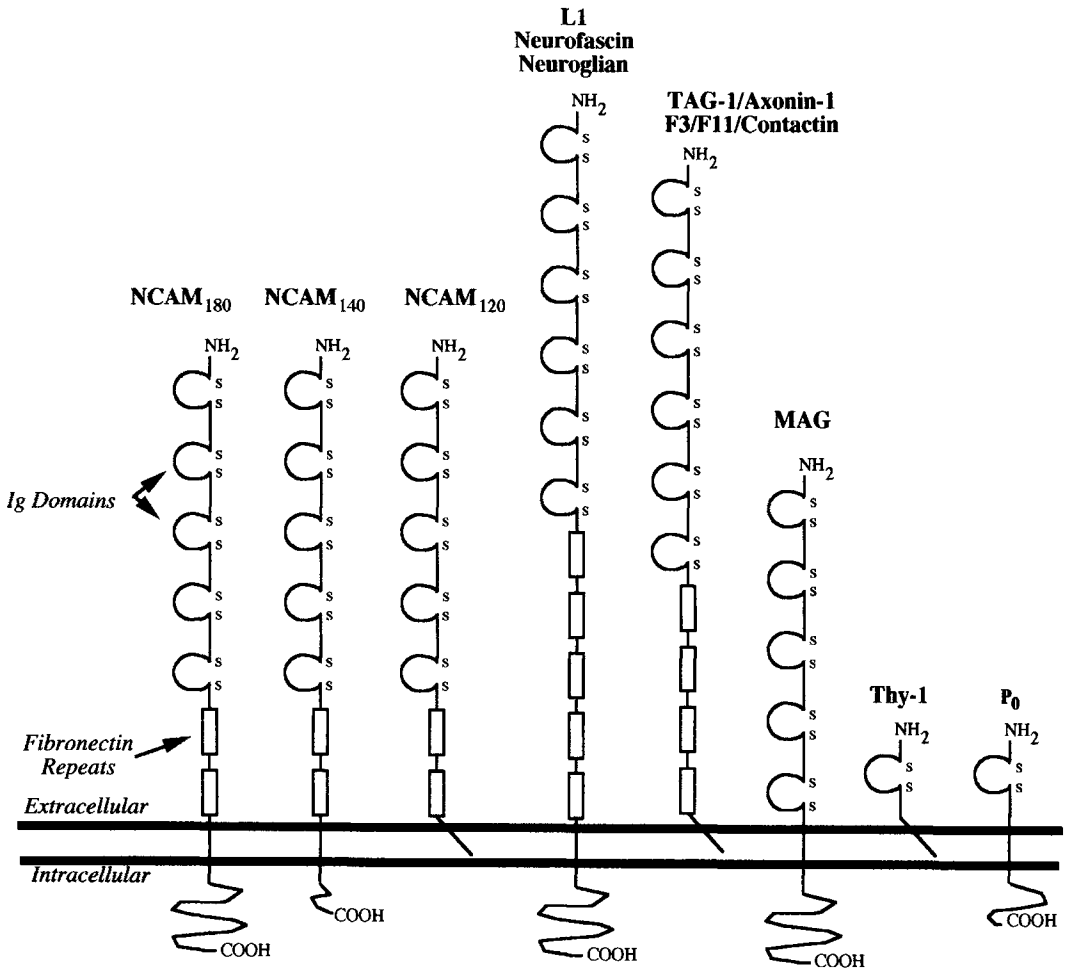

Fig. 4. Outline structures of members of the immunoglobulin supergene family of neural cell surface glycoproteins.

All three NCAM isoforms have identical extracellular domains that consist of five Ig domains and two fibronectin type III domains (Cunningham et al., 1987). Each of the five Ig domains (Ig1–Ig5) is associated with a specific function (Fig. 5). Ig1 (the domain at the N-terminal end) is thought to play a role in the mediation of cell adhesion and neurite outgrowth (Frei et al., 1992), whereas Ig2 has a 17-amino-acid heparin sulfate-binding site (Reyes et al., 1990). In addition, Ig1 and Ig2 may be involved in a double-recipricol binding interaction, the possibility of which is supported by the three-dimensional structures of the domains (Kiselyou et al., 1997; Thomsen et al., 1996). In addition, both domains can bind collagen type I via heparin (Kiselyov et al., 1997). Ig3 binds homophilically to other NCAM molecules via a decapeptide sequence from Lys-243 to Glu-252 (Rao et al., 1994). However, each of the other four individual domains in solution is capable of binding at a different site (Ig1 and Ig5 bind, as do Ig2 and Ig4) and antibodies to any NCAM domain will inhibit binding (Siu, 1995; Ranheim et al., 1996). Hence, although Ig3 appears to be the dominant force in NCAM–NCAM binding, the other domains may also play a role in

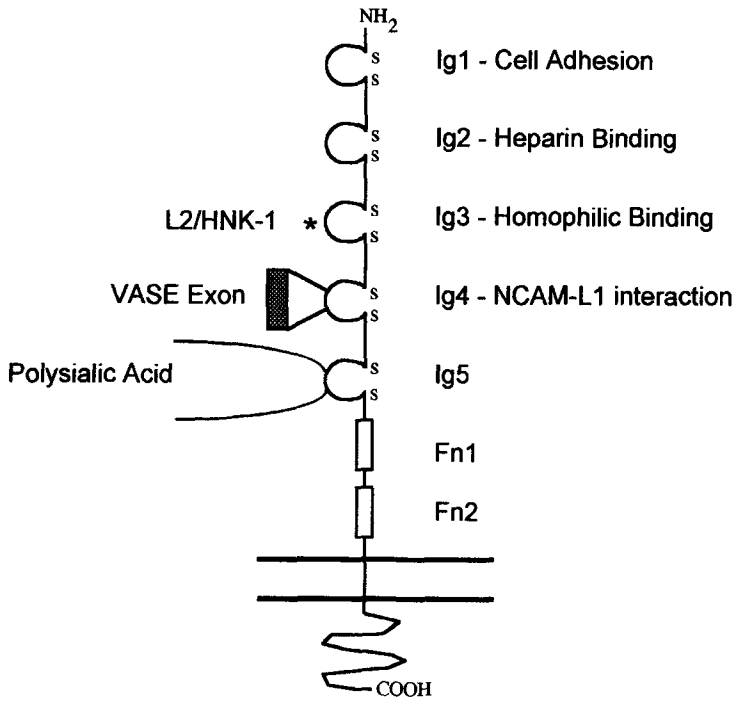

Fig. 5. Structural and functional domains of the neural cell-adhesion molecule, NCAM.

maintaining or stabilizing this interaction. The Ig4 domain contains the variable alternatively spliced exon (VASE) and may also play a role in NCAM-L1 interaction (Kadmon et al., 1990a), whereas Ig5 contains the site for the attachment of the N-linked polysialic acid oligosaccharide chain (Nelson et al., 1995). The two fibronectin type III domains have also been proposed to play a role in NCAM-mediated adhesion, possibly in a heterophilic binding fashion (Kasper et al., 1996).

The VASE exon, present in Ig4, is a variably spliced 30-base sequence that codes for a 10-amino-acid insert that is expressed primarily in mature neurons (Doherty et al., 1992). It serves to decrease the ability of the protein to stimulate neurite outgrowth, possibly by increasing the stability of NCAM homophilic interactions (Saffell et al., 1994). This inhibitory property would appear to be caused by the amino acid sequence itself rather than the complete VASE-NCAM protein, as an inhibitory effect was also observed when it was expressed as part of a chimeric F3 glycoprotein (Arce et al., 1996). This inhibition of neurite outgrowth by VASE may also be a result of a decrease in the ability of NCAM to activate the FGF receptor and may thus explain the poor regenerative ability of mature CNS neurons that express it when compared with peripheral neurons that do not express VASE (Walsh et al., 1992; Bruses et al., 1995).

The cytoplasmic domain of the transmembrane forms of the protein is a prerequisite for the adhesion-mediated promotion of neurite outgrowth by NCAM as the GPI-linked isoform does not exhibit this property (Saffell et al., 1995). These results have been confirmed by a gene targeting strategy that replaced the membrane-associated form of the protein with a secreted form, resulting in a dominant embryonic lethality (Rabinowitz et al., 1996).

In addition to its homophilic interactions, NCAM may interact with L1 in a *cis* fashion by a carbohydrate-dependent mechanism mediated by oligomannoside oligosaccharide

chains (Kadmon et al., 1990a, b; Horst Korte et al., 1993). Furthermore, NCAM can also interact with elements of the extracellular matrix including collagen (Probsteimes et al., 1992; Breen et al., 1991), heparin sulfate proteoglycans, and chondroitin sulfate proteoglycans (Reyes et al., 1990; Storms et al., 1996; Grumet et al., 1993). The heparin binding domain present in Ig2 also acts to mediate NCAM adhesion to elements of the extracellular matrix (Cole and Glaser, 1986; Werz and Schachner, 1988).

In a similar fashion to N-cadherin, NCAM stimulates adhesion-mediated neurite outgrowth via an erbstatin-sensitive tyrosine kinases-phospholipase C gamma cascade (Williams et al., 1994a, b), with the subsequent activation of L- and N-type calcium channels (Volberg et al., 1992; Doherty and Walsh, 1996). In addition, membrane-bound $NCAM_{140}$ specifically interacts with the src tyrosine kinase p59(fyn), which is involved in growth cone migration, and the focal adhesion kinase p125(fak) which mediates integrin-dependent signaling (Beggs et al., 1997). This complexation of $NCAM_{140}$ with p125(fak) and p59(fyn) may play a pivotal role in the modulation of neurite outgrowth. Further evidence, however, suggests that protein phosphatases may also play a role in NCAM- and L1-associated neuronal growth, proposing a delicate balance between the kinase and phosphatase activities at the level of the growth cone (Klinz et al., 1995).

Both during development and coincident with plastic events in the adult CNS, NCAM can exist in a heavily glycosylated (sialylated) form with the presence of polysialic acid side chains (Fig. 3A) (*see* Polysialic Acid). This serves to decrease the homophilic-binding capacity of the protein (Moran and Bock, 1988) and the precise spatiotemporal regulation of this group ensures the correct neuronal positioning prior to synapse formation. Animals with an upset in PSA-NCAM regulation exhibit severe deficits in the CNS cytoarchitecture (Edelman and Chuong, 1982). In addition, NCAM also contains O-linked oligosaccharide chains (Walsh et al., 1989) and a subset of proteins express the L2/HNK-1 epitope (Fig. 3B), which may play a role in the modulation of the adhesive properties of the protein backbone (*see* L2/HNK-1).

L1

L1 (also termed NgCAM and NILE) is a transmembrane glycoprotein containing 6 Ig-like domains and 5 fibronectin-type-III repeat domains (Fig. 4) (Prince et al., 1991; Moos et al., 1988), the gene for which is located on the X-chromosome (Kenwrick et al., 1996). The protein plays a pivotal role in adhesion associated with both neural cell development and synaptogenesis (Keihauer et al., 1985), with mutations of the protein resulting in alterations in the developmental process (*see* Glycoprotein Mutations; Schachner, 1995). L1 exists as a 200 kDa membrane-bound protein that can be broken down by proteolysis to yield a number of smaller fragments (Sadoul et al., 1988). A splice variant of L1 containing a 12 base pair cytoplasmic insert has also been identified (Reid and Hemperly, 1992). L1 mediates its adhesive functions largely via homophilic binding mechanisms that do not appear to be carbohydrate-dependent (Miura et al., 1992; Zhao and Siu, 1995) and uses several overlapping domains that show some regional specialization within the CNS (Appel et al., 1993; Holm et al., 1995). In addition, it has been demonstrated to interact with other proteins including integrins (Montgomery et al., 1996; Kadmon and Alterogt, 1997; Ebeling et al., 1996), VLA-5, the fibronectin receptor (Ruppert et al., 1995), proteoglycans (Milev et al., 1995; Friedlander et al., 1994), and galectin-3, a β-galactoside-binding animal lectin (Probsteimer et al., 1995). L1 may also interact with the cytoskeleton via ankyrin, a spectrin-binding protein present on the cytoplasmic surface of the cell membrane (Davis and Bennatt, 1994; Dubrevil et al., 1996). In addition to its *trans* interactions with proteins to mediate cell adhesion, L1 has been proposed to interact in a *cis* fashion with adjoining proteins to form a functional adhesive or signal transduction-mediat-

ing complex. It can bind to NCAM within the membrane via an oligomannosidic carbohydrate group present on L1 (Kadmon et al., 1990a, b; Horst Korte et al., 1993; Schmitz et al., 1993) and this has been proposed to play a role in the modulation of cell adhesion by an "assisted homophilic interaction" (Kadmon et al., 1990a; Feizi, 1994). Other proteins with which L1 may interact in the same membrane include members of the integrin family, CD9 (Schmidt et al., 1996), and the heat-stable antigen, nectadrin (Kadmon et al., 1995).

In a manner similar to both *N*-cadherin and N-CAM, L1 has been demonstrated to play a role in adhesion-mediated signal transduction and the stimulation of neurite outgrowth (Doherty et al., 1995). However, the $pp60^{c\text{-}src}$ nonreceptor protein kinase has also been proposed to be involved in the intracellular signaling pathway of L1-mediated neurite outgrowth (Ignelzi et al., 1994). One of the key domains involved in this process lies between the fibronectin-type-III repeat domains 2 and 3, and a synthetic peptide corresponding to amino acids 818–832 stimulates neurite outgrowth by increasing cellular calcium levels and stimulating phosphatidyl inositol turnover (Appel et al., 1995). Recent studies have identified two residues in the cytoplasmic domain of the protein that can be phosphorylated. Ser_{1152} provides a target for the actions of the S6 kinase, p90(rsk), whereas casein kinase II phosphorylates Ser_{1181} (Wong et al., 1996a, b) with both of these residues being phosphorylated in vivo in the developing brain. Phosphorylation may serve to modulate aspects of L1 function such as adhesion or signal transduction.

Other Members of the Ig Superfamily

Neurofascin/neuroglian and Bravo/NrCAM are two axon-associated transmembrane glycoproteins belonging to the L1 subgroup of the Ig superfamily, each containing 6 Ig domains and 5 fibronectin-type-III repeat domains (Lane et al., 1996; Grumer et al., 1991; Kayyem et al., 1992). Neurofascin consists of a number of proteins, generated by alternative splicing of a single gene, of molecular weights 185, 160, and 110–135 kDa, and is extensively O- and *N*-glycosylated (Volkmes et al., 1992). Bravo/NrCAM is a 145 kDa glycoprotein with a short cytoplasmic domain that may exist as a heterodimer structure composed of a 140 kDa alpha chain and a 60 kDa beta chain, with the latter being derived by proteolysis from the larger polypeptide (Kayyem et al., 1992). In addition to their facility for mediating homophilic interaction, experiments using Fc-chimeric constructs of the proteins have demonstrated that there is a direct heterophilic interaction, probably mediated by the Ig domains, between Bravo/NrCAM and neurofascin during axonal extension (Volkmer et al., 1996). Furthermore, both of these proteins also display ankyrin-binding activities in their cytoplasmic domains, proposing a role in the stabilization of cell–cell contacts (Davis and Bennatt, 1994; Davis et al., 1996), and while the generation of a GPI-linked form of neuroglian resulted in the absence of protein interaction with ankyrin (Dubrewil et al., 1996), this did not inhibit its ability for calcium-independent homophilic binding (Hortsch et al., 1995).

The mouse F3 glycoprotein (and its chicken homolog contactin/F11) is a 130 kDa axon-associated cell-adhesion molecule (AxCAM) that is linked to the membrane via a glycosylphosphatidyl inositol group (Fig. 4) and both the membrane-bound and soluble forms of this protein serve to mediate cell adhesion and promote neurite outgrowth (Reid et al., 1994; Gennarini et al., 1991; Durbec et al., 1992). Its distribution in the CNS is restricted and, for example, it is only expressed by the parallel fibers within the cerebellum. Coimmunoprecipitation studies have suggested an interaction between F3 and L1 (Brummendorf et al., 1993; Olive et al., 1995) and, in addition, it is capable of binding to NrCAM and to the extracellular matrix glycoproteins restrictin and J1/tenascin. The adhesion sites have been partially mapped with the L1-binding site residing in Ig domains I and II and restrictin-binding site in domains II and III, although the fibronectin-type-III repeat domains may also

play a modulatory role (Brummendorf et al., 1993; Durbec et al., 1994; Pesheva et al., 1993). The binding site for NrCAM has been localised to the second or third Ig domain of the protein (Morales et al., 1993).

TAG-1/axonin-1 is another glycosylphosphatidylinositol-linked AxCAM consisting of six Ig domain repeats and four fibronectin type-III domains (Fig. 4) that can also exist in a secreted form, with the latter playing a role as a neurite-promoting substrate (Zvellig et al., 1992; Stoeckli et al., 1991; Hasler et al., 1993). TAG-1 can mediate homophilic binding (Rader et al., 1993), and it has also been demonstrated to exhibit a high-affinity interaction with a number of chondroitin proteoglycans including neurocan and phosphocan, with this interaction being dependent on the presence of the chondroitin group of the proteoglycans. Furthermore, it may also interact with NCAM, L1, NrCAM, and specific integrins in a heterophilic-binding manner (Felsenfeld et al., 1994; Milev et al., 1996; Buchstaller et al., 1996; Suter et al., 1995). L1 binding is modulated by the four amino terminal Ig domains of axonin-1 and the deletion of the fifth or sixth domains of the membrane-bound form of the protein actually increases the binding strength (Rader et al., 1996). The different adhesion ligands may be associated with specific intracellular signaling mechanisms that may be modulated following protein–protein interaction. A *cis* heterophilic interaction between L1 and axonin results in the formation of protein clusters within the membrane (Stoeckli et al., 1996) with a subsequent decrease in the axonin-1-associated *fyn* kinase activity and an increase in the L1-associated casein kinase II, and these changes in enzyme activities may serve as adhesion-dependent growth-associated cell signals (Kunz et al., 1996). Each of the constituent AxCAMs exhibit a unique spatiotemporal expression pattern in the CNS during development, suggesting that they each play an individual role in the generation of specific neuronal networks (Yoshihara et al., 1994; Faiver Sarrailh, 1993).

Thy-1 is a GPI-linked glycoprotein containing one Ig domain (Fig. 4) that forms clusters within the membrane to modulate adhesion-dependent neurite outgrowth. The protein function is dependent on its GPI anchor and is not observed in a chimeric protein containing the transmembrane domain of $NCAM_{140}$ and the extracellular domains of Thy-1 (Tiveron et al., 1994). Thy-1 can also serve to stimulate neurite outgrowth in PC12 cells and this is mediated by a calcium influx through both N- and L-type calcium channels following G protein activation (Doherty et al., 1993).

One of the principal components of peripheral myelin, accounting for over 50% of the total protein content, is the 30 kDa P_0 glycoprotein (Fig. 4), which plays a key role in the compaction of the myelin sheath (Martini et al., 1995). This transmembrane protein can also exhibit neurite-outgrowth promotion activity in the dorsal root ganglia (Yazaki et al., 1994). P_0 mediates both homophilic (Filbin et al., 1990) and heterophilic (Schneider Schaulies et al., 1990) interactions for which an intact cytoplasmic protein domain of the protein is essential (Yazaki et al., 1992), this being suggestive of a potential interaction between the protein and elements of the cytoskeleton (Wong and Filbin, 1994). The protein glycosylation state is also important for P_0 function and the exchange of complex N-linked oligosaccharides with an oligomannose sugar chain greatly decreased its adhesivity (Filbin and Tennekoon, 1991, 1993). A subset of P_0 proteins also expresses the L2/HNK-1 carbohydrate epitope (Fig. 3B), which modulates its adhesive function (Badache et al., 1992; Griffith et al., 1992; Bollensen and Schachner, 1987).

The myelin-associated glycoprotein (MAG) is a 110 kDa transmembrane protein containing 5 Ig domains (Fig. 4), which mediates the interaction between myelinating glial cells and neuronal axons (Fruttiger et al., 1995). It is also thought to be a major inhibitor of axon regeneration in the CNS, and it is capable of promoting neurite outgrowth from newborn dorsal root ganglion cells (Mukhopadhyay et al., 1994). MAG is capable of binding to receptor

proteins on neuronal cells as well as with collagen and heparin and using specific antibodies, the Ig domain III has been associated with binding to neuronal cells, whereas domains I, II, and III bind to collagen and domains II and III with heparin (Meyer Franke et al., 1995; Bachman et al., 1995). MAG also binds to a limited set of structurally related gangliosides, including GQ1b, GT1b, and GD1a, which are present on myelinated neurons (Yang et al., 1996) and to galectin-3, a β-galactoside-binding animal lectin (Probsteimer et al., 1995). MAG expresses high levels of the L2/HNK-1 carbohydrate epitope (Fig. 3B), although the levels of the epitope are regulated independently from that of the protein backbone (Pedraza et al., 1995; Low et al., 1994; Burger et al., 1993). Furthermore, MAG binds to oligosaccharides terminating in α2,3-linked sialic acid, thus classifying it as a member of the I-type lectin family (Powell and Varki, 1995). MAG is also tyrosine phosphorylated and binds to the *fyn* tyrosine kinase within the membrane, suggesting that it may play a role in adhesion-mediated signal transduction (Jaramillo et al., 1994; Bhat, 1995).

Other Adhesion Glycoproteins

The Amyloid β Precursor Protein (AβPP)

AβPP is an integral transmembrane protein containing one membrane-spanning domain and a 47-residue cytoplasmic domain (Kang et al., 1987) that is expressed in almost all neural and nonneural mammalian tissues, with the highest degree of expression found in the brain and kidney (Selkoe, 1994). In addition to the membrane-bound holoprotein, AβPP can be cleaved proximal to the membrane to generate a secreted form of the protein ($A\beta PP_s$). There are three primary isoforms of the protein derived by alternative splicing of a single gene located on chromosome 21: $A\beta PP_{695}$, $A\beta PP_{751}$, and $A\beta PP_{770}$ (subscripts referring to the amino acid number) (Fig. 6; Kang et al., 1987). The two larger isoforms of the protein contain a Kunitz-type protease-inhibitor domain spliced into the extracellular region of the protein and $A\beta PP_{770}$ contains an additional 19-amino-acid OX-2 domain (Ponte et al., 1988; Kitaguchi et al., 1988; Tanzi et al., 1988) with the secreted forms being identical to protease nexin II (Oltersdorf et al., 1989). Other members of the AβPP family include L-AβPP, which lacks exon 15 of the AβPP gene and is only expressed in nonneuronal cells (Sandbrink et al., 1994; Konig et al., 1992) and the amyloid precursor-like proteins 1 and 2 (APLP1 and APLP2) which do not contain the Aβ peptide region (Wasco et al., 1993; Sandbrink et al., 1994). AβPP migrates through an SDS-PAGE electrophoretic gel as a group of polypeptides whose molecular weights range from 100–140 kDa, the variety in band size representing both the different molecular weights of the isoforms as well as differentially posttranslationally modified forms of the protein. The $A\beta PP_{751}$ isoform is the most widely expressed throughout the body, whereas $A\beta PP_{695}$ is only expressed in neurons, in which it is the predominant isoform (Neve et al., 1988; Spillantini et al., 1989).

AβPP is both *N*- and *O*-glycosylated (Weidemann et al., 1989), and the presence of glycosaminoglycan side chains generate a chondroitin sulphate proteoglycan form of a higher molecular weight (Pangalos et al., 1995; Shioi et al., 1993). There are two potential N-linked sites (Asn_{467} and Asn_{496}), although available evidence suggests that only the former site is occupied (Pahlsson et al., 1992) by a bi- or tri-antennary complex oligosaccharide (Fig. 1A) with a fucosylated tri-mannosyl core and a terminal sialic acid residue (Pahlsson et al., 1992; Saito et al., 1995; Dichgans et al., 1993). However, it is likely that a number of different glycoforms of the protein exist (Saito et al., 1995; Simons et al., 1995; Moya et al., 1994) and protein glycosylation appears to play a key role in AβPP processing and function (Pahlsson and Spitalnik, 1996).

The cytoplasmic domain of AβPP also contains eight putative phosphorylation sites that can be phosphorylated in vitro by protein kinase C, Ca^{2+}/calmodulin-dependent kinase, $p34^{cdc2}$ kinase, and GSK-3β but not by MAP

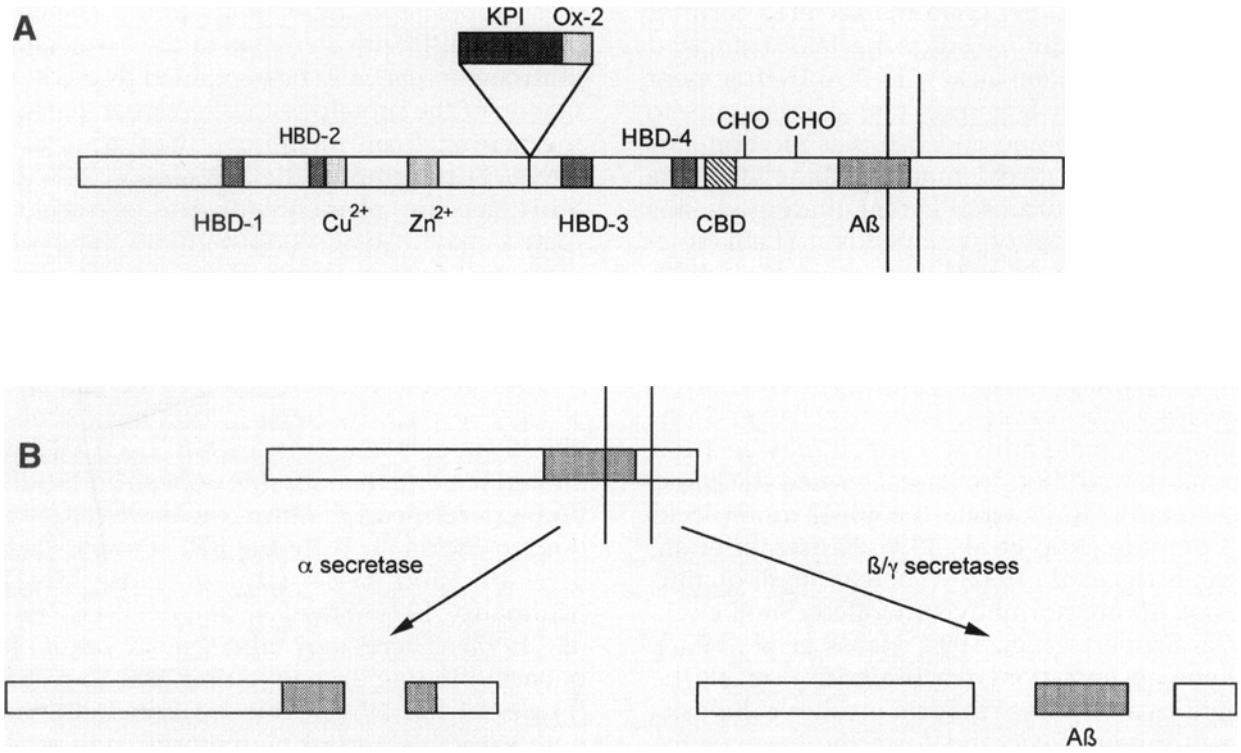

Fig. 6. (**A**) The general structure of AβPP indicating the known functional domains. HBD = heparin-binding domain; KPI = Kunitz protease inhibitory domain; CBD = collagen binding domain; CHO indicated potential N-linked glycosylation sites.

kinase, and phosphorylation may be important in modulating the processing pathway of the protein (Gandy et al., 1988; Suzuki et al., 1994; Aplin et al., 1996). However, the PKC-stimulation of $A\beta PP_s$ secretion does not appear to be caused by a direct action on the protein but rather the phosphorylation of other substrates that control $A\beta PP_s$ generation (Hung and Selkoe, 1994). Because of its transmembrane structure, AβPP has been proposed to play a role as a receptor. There is a region within the cytoplasmic domain capable of complexing with GTP-binding protein that coincides with the potential phosphorylation sites (Nishimoto et al., 1993; Okamoto et al., 1995), thus providing a mechanism by which the functionality of the AβPP receptor may be modulated. Subsequently, additional AβPP-binding proteins have been identified with which AβPP may interact within the membrane with functional consequences. AβPP-BP1 is a 59 kDa protein that exhibits 61% homology with the *Arabidopsis* AXR1 gene, which plays a role in the transduction of the response to auxin and is related to the ubiquitin-activating enzyme, E1 (Chow et al., 1996). AβPP has also been demonstrated to interact with the neuronal protein Fe65, which is a homolog of protein X11. This protein contains one or more phosphotyrosine-binding (PTB) domains that are believed to function in signal transduction (McLoughlin and Miller, 1996; Guenette et al., 1996).

Within the AβPP structure there is a 42 amino acid sequence termed the Aβ region, which is located partially within the membrane (amino acids 29–42), and partially in the extracellular space (amino acids 1–28). The membrane-bound AβPP can be processed in either of two primary pathways: It can be cleaved within the Aβ region (at residue 16) by

a α-secretase to generate the secreted form of the protein, AβPP$_s$ (Fig. 6B). This truncated form of the protein lacks a 17–18-kDa fragment of the carboxyl terminus that corresponds to the transmembrane and cytoplasmic domains of the protein (Weldemann et al., 1989). The portion of mature AβPP that undergoes this processing is cell-type dependent (Leblanc et al., 1996, 1997). In addition, there have been reports of the secretion of the full-length form of AβPP (Vassilacopoulou et al., 1995). Alternatively, AβPP can be endocytosed in lipid vesicles to be broken down by the endosomal/lysosomal pathway. Here, it may be acted upon by two other proteases, termed the β and γ secretases, to generate the 40–42-amino-acid Aβ peptide (Koo et al., 1996; Yamazaki et al., 1996; Estus et al., 1992). Whereas small quantities of Aβ are normally generated (Shoji et al., 1992; Seubert et al., 1992; Haass et al., 1992), when concentrations reach a critical level, the peptide can coalesce to form insoluble deposits that are neurotoxic and form the basis of the amyloid plaques characteristic of Alzheimer's disease pathology (Pike et al., 1993).

AβPP exhibits a punctate membrane-staining pattern in neuronal cells, particularly in static rather than actively motile portions of the neurites, suggesting that it may play a role in the mediation of cell adhesion by the generation of adhesion patches (Jung et al., 1996; Storey et al., 1996a, b; Yamazaki et al., 1995; Shivers et al., 1988). Initial studies using antibodies directed against the extracellular domain of the protein demonstrated an inhibition of both cell–cell interaction and cell adhesion to elements of the extracellular matrix (Breen et al., 1991; Schubert et al., 1988). Further studies have demonstrated that AβPP can interact with numerous elements of the extracellular matrix including collagen (Beher et al., 1996; Breen, 1992), laminin (Kibbey et al., 1993; Multhaup et al., 1992), fibronectin, entactin (Narindras-Orask et al., 1995), heparin sulfate proteoglycans (Narindrasorasak et al., 1991; Williamson et al., 1995), and glycosaminoglycans (Multhaup, 1994), with the individual AβPP isoforms displaying differential adhesive properties (Gillian et al., 1997). The adhesion of AβPP with elements of the extracellular matrix may partially be explained by a colocalization of the protein with selective integrins in the neuronal cell membrane (Yamazaki et al., 1997). Furthermore, the interaction of AβPP with specific elements of the extracellular matrix may also serve to regulate the expression and/or processing of the protein (Breen and Ronayne, 1994; Breen, 1995; Monning et al., 1995).

AβPP-mediated adhesion may be mediated, at least in part, by heparin binding (Small et al., 1994) and the protein has been demonstrated to contain at least four heparin-binding domains termed H-I (amino acids 96–110), H-II (amino acids 131–166), H-III (amino acids 316–346), and H-IV (amino acids 382–447; Multhaup, 1994; Small et al., 1994; Clarris et al., 1997). There may also be an additional heparin-binding domain within the Aβ region (Fraser et al., 1992). This heparin binding is both saturable and of high affinity and is also displayed by the homologs APLP1 and APLP2 and by L-AβPP (Multhaup, 1994; Mulhaup et al., 1995) and it may be modulated by zinc (Multhaup et al., 1994; Bush et al., 1994). The exact physiological role of zinc in AβPP function is unknown, but it has been proposed to act as a local cofactor modulating the interaction between cell-surface glycoproteins and elements of the extracellular matrix to regulate neurite outgrowth. AβPP has also been demonstrated to bind copper, which may influence the conformation, stability and extracellular matrix binding of the protein (Hesse et al., 1994). In addition, AβPP is capable of reducing Cu(II) to Cu(I) (Multhaup et al., 1996).

The secreted form of the protein, AβPP$_s$, may also serve to mediate both cell adhesion and adhesion-stimulated neurite outgrowth and it has been demonstrated to interact with elements of the extracellular matrix in an isoform-specific manner to provide a substrate for cell adhesion and the promotion of neurite outgrowth (Schubert et al., 1988; Koo et al., 1993; Qiu et al., 1995; Klier et al., 1990). AβPP and APLP-2 can exist as chondroitin sulfate

proteoglycans, termed appican, which are derived from L-AβPP/L-APLP-2 (Pangalos et al., 1995; Shioi et al., 1996; Thinakaran et al., 1995), thus suggesting that the lack of exon 15 is a prerequisite for the binding of the glycosaminoglycan chain. The $A\beta PP_s$ component of the extracellular matrix has also been demonstrated to bind to distinct elements of the cell membrane, suggesting the possible existence of a cell-surface AβPP receptor (Ninomiya et al., 1994) and although this site may be distinct from the heparin-binding site(s) of the protein (Ninomiya et al., 1994), heparin may also play a role in the mediation of $A\beta PP_s$-mediated adhesion. For example, when B103 cells (which do not express endogenous AβPP) are incubated with $A\beta PP_s$, both its binding to the cells and its ability to induce neurite extension is decreased in a dose-dependent manner by coincubation with heparin or heparitinase.

In addition to its role in the modulation of cell adhesion, $A\beta PP_s$ exhibits neurotrophic, mitogenic, and neuroprotective potentials and it may play a key role in neural plasticity, both alone and by acting to modulate the actions of other neurotrophic factors including nerve growth factor (Majocha et al., 1994; Mattson, 1994). The down-regulation of AβPP inhibits neurite outgrowth in vitro (Alling Vant et al., 1995) and there is some evidence to suggest that neurite outgrowth may be controlled, at least in part, by a balance between the constituent AβPP isoforms with the KPI domain of the protein playing a significant role (Diaz-Nido et al., 1991; Hayashi et al., 1994). This is in good agreement with previous studies that have postulated a delicate balance between proteases and protease inhibitors at the level of the growth cone (Monard, 1988).

$A\beta PP_s$ may mediate its neuroprotective effect by binding to a cell-surface receptor and activating second-messenger system(s) within the cell. [^{125}I]-labeled $A\beta PP_s$ binds to B103 cells (that do not express endogenous AβPP) at a density of 10^5 binding sites per cell with an affinity of 20 ± 5 n*M* (Saitoh and Roch, 1995). This binding is sequence specific and a pentapeptide neurite-promoting region of AβPP has been identified (Jin et al., 1994; Ninomiya et al., 1993; amino acids 330–333) that acts to increase synaptic density and memory retention in vivo (Roch et al., 1994). AβPP also acts to protect against toxic attack by such agents as glutamate and ischemic insults (Smithswintosky et al., 1994; Mattson et al., 1993) as well as by the aggregated Aβ peptide (Goodman and Mattson, 1994) by stabilizing the neuronal calcium homeostasis (Mattson, 1994). Although the exact mechanisms underlying this effect have yet to be identified, a number of second-messenger systems have been implicated in the process including the activation of guanylate cyclase (Barger and Mattson, 1995; Barger et al., 1995), the induction of phosphatidylinositol turnover (Jin et al., 1994), the mitogen-activated protein (MAP) kinase system (Greenburg et al., 1995), and the suppression of neuronal activity by hyperpolarization following the activation of charybdotoxin-sensitive potassium channels (Furukawa et al., 1996).

Carbohydrate Epitopes

Whereas protein glycosylation in general exerts a major influence on the structure and subsequent function of the protein backbone, particular carbohydrate epitopes have been identified on neural proteins that play a particular role in the modulation of cell function and particularly cell–cell interaction (Schachner and Martini, 1995).

Polysialic Acid

Polysialic acid (PSA) is a linear oligosaccharide of multiple α2,8-linked sialic acid residues (up to 100 residues per chain) that may be attached to tri- and tetra-antennary complex N-linked oligosaccharides (Fig. 3A; Finne, 1982; Kudo et al., 1996). In mammalian cells, PSA is expressed exclusively on NCAM (Finne et al., 1983), although it was originally detected in aquatic animals and certain strains of *E. coli* (Reglero et al., 1993). PSA is attached to a terminal α2,3 sialic acid residue on N-linked oligosaccharide chains linked to Asn_{459} and Asn_{430}

present on the Ig5 domain of NCAM (Fig. 5) and mutation of either of these residues will reduce or abolish NCAM polysialylation (Nelson et al., 1995). The generation of PSA is controlled by two polysialosyltransferase enzymes—PST and STX (Easton et al., 1995; Kojima et al., 1996), which act to elongate the polysialic acid chain from an α2,3-linked sialic acid attachment point (*see* N-Linked Biosynthesis). The expression of the STX enzyme is developmentally regulated (Angata et al., 1997) and it is this enzyme that directs NCAM PSA biosynthesis during neuronal differentiation (Kojima et al., 1996a). A core α1,6-linked fucose residue may also be a prerequisite for PSA biosynthesis (Kojima et al., 1996b), and it was shown that the *cis*-Golgi removal of the high-mannose residues occurs before polysialylation, thus suggesting that the PSA addition occurs either at or beyond the *medial*-Golgi (Alcaraz and Goridis, 1991; Schedegger et al., 1994), but prior to the insertion of the protein into the synaptic membrane (Breen and Regan, 1986; Breen et al., 1987). Whereas neither Ig4 or the first fibronectin type III repeat domain is polysialylated, both of these neighboring domains are required for polysialylation to occur (Nelson et al., 1995). Taken together, Ig5 and the adjacent domains are spatially a compact unit, so all three may act to form a pocket for the action of PST and/or STX to elongate the sialic acid chain.

PSA is considered to play a pivotal role in the modulation of both cell–cell adhesion and cell interaction with elements of the extracellular matrix, both during neuronal development, as well as in synaptic plasticity in the adult (Rutishauser and Landmesser, 1996; Acheson et al., 1991) and the strength of the NCAM-NCAM binding is inversely dependent on the level of bound SA (Moran and Bock, 1988). Whereas the exact effect of PSA has not been determined, it is likely to act by increasing the intracellular space between opposing synaptic membranes and thus preventing glycoprotein interaction associated with synaptogenesis (Yang et al., 1992). It may also act however in a *cis* manner to modulate the interaction between proteins within the same membrane, such as that described for NCAM and L1 (Fig. 7; Kadmon et al., 1990b).

The primary function of the polysialylated form of NCAM (PSA-NCAM) is to regulate structural plasticity and immature CNS regeneration. The expression of PSA-NCAM is developmentally regulated, with the expression of this form of the protein being dominant during the embryonic stages of CNS and peripheral development, but not during other phases (Fryer and Hockfield, 1996). The factors regulating PSA expression are unclear but cell–cell interaction may play a role in the downregulation of PSA expression following synaptogenesis and there is a good temporal correlation between the rate of synapse formation and the loss of PSA expression (Bruses et al., 1995). PSA expression may also be activity-related and an increase in intracellular calcium levels, either by the activation of NMDA receptors or voltage-gated ion channels, with a subsequent activation of protein kinase C, is necessary for the expression of PSA-NCAM (Wang et al., 1996; Rafuse and Landmesser, 1996).

During CNS development, growth cones are guided by many permissive and/or inhibitory mechanisms. The expression of PSA-NCAM is thought to regulate growth cone behavior and cell migration and also to regulate L1-mediated axon fasciculation in a manner independent of its own adhesive properties. In addition to its role in axonal guidance and elongation, PSA-NCAM is also present on the axonal surface where it serves to promote neuritic elongation and axonal fasciculation (Seki and Arai, 1993; Muller et al., 1994). Although the immature CNS can regenerate after injury, this ability is largely lost during the later phases of development (Shewan et al., 1995). The damaged adult CNS only has the ability to undergo limited regeneration and PSA-NCAM is thought to be involved to some degree in the developmental events that are recapitulated during CNS regeneration (Aubert et al., 1995).

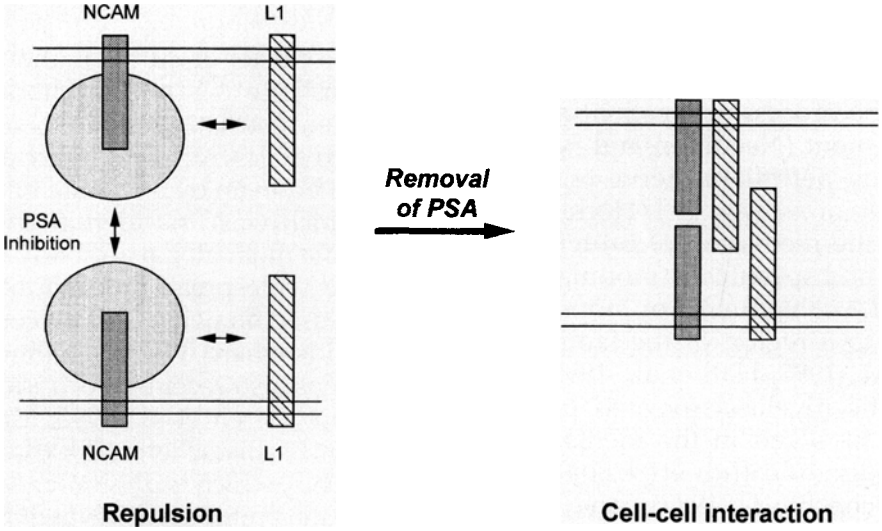

Fig. 7. Diagrammatic representation of the effect of polysialic acid, represented by the shaded circle, on the cis and trans interaction of NCAM. The removal of the PSA results in both NCAM homophilic binding as well as cis interaction between NCAM and L1.

L2/HNK-1

The L2/HNK-1 carbohydrate epitope (Abo and Balch, 1981; Kruse et al., 1984) is a developmentally regulated oligosaccharide (Breen, 1989; Chou et al., 1991; Schwarting et al., 1987) that has been detected on a large number of cell-surface glycoproteins including NCAM, L1, MAG, P_0, integrins, and fibronectin (Pesheva et al., 1987; Kruse et al., 1984; Noronha et al., 1986; Bigliardi et al., 1995). It is also expressed on glycolipids (Chou et al., 1985; Jungalwala et al., 1992) and on proteoglycans (Gowden et al., 1989). Initially, it was characterized on glycolipids as a complex oligosaccharide containing a terminal sulfated glucuronic acid group (Fig. 3B; Chou et al., 1986). Whereas the degree of sulfation is critical for L2/HNK-1 function, evidence suggests that the structure of the oligosaccharide on glycoproteins may vary somewhat depending on the protein backbone. Initial studies on the ependymin-adhesion glycoprotein in goldfish (Shashoua, 1991) reported the presence of 3-sulfoglucuronosyl residues on the L2/HNK-1 (Shashoua et al., 1986), whereas more recent studies on the myelin-associated protein, P_0, suggested that there was no evidence for the presence of a glucuronic acid group, but instead that the oligosaccharide may contain terminal *N*-acetylneuraminic acid groups (Field et al., 1992).

The expression of the oligosaccharide is regulated independently of its protein backbone (Low et al., 1994; Kruse et al., 1984) and it has been proposed to play a role as an adhesion ligand (Keihauer et al., 1985; Kunnemond et al., 1988), with both the terminal sulfate groups and the neolactosyl-type backbone each playing a key role in determining the adhesive properties of the sugar chain (Kunnemond et al., 1988; Schmitz et al., 1994). There is a significant variation in L2/HNK-1 expression levels, for example on MAG, both at tissue and species levels (Low et al., 1994), and the available evidence suggests that its expression may be regulated independently of the protein backbone following the activation of second-messenger systems (Pedraza et al., 1995).

In certain brain regions, L2/HNK-1 may serve as an extracellular scaffold to support

neurite outgrowth (Layer and Kaulich, 1991). The lipid-bound epitope has also been demonstrated to modulate cell interaction, specifically in the process of myelination both during development (Needham and Schnaar, 1993) and during peripheral nerve regeneration (Martini et al., 1994). L2/HNK-1 also plays a role in the mediation of protein–protein interaction and specifically modulates the binding of the L1 constituents of mouse cerebellar neurons to a region of the laminin α1 chain (Hall et al., 1997; Hall et al., 1995). It is expressed by the myelin-associated proteins P_0, where it is involved in the mediation of homophilic binding (Griffith et al., 1992; Bollensen and Schachner, 1987) and MAG (Burger et al., 1993) where a decrease in the level of the carbohydrate epitope may be associated with the defect in myelination associated with the quaking mouse (Bartoszewicz et al., 1995). In addition to its role in the modulation of P_0 homophilic binding, there are also reports of a high-affinity, saturable, calcium-dependent binding site for L2/HNK-1, which may be involved in myelination or myelin maintenance (Needham and Schnaar, 1993).

L3 and L4 are additional carbohydrate epitopes expressed in the nervous system that were originally identified in a group of mannosidic leech glycoproteins (Zipser and Cole, 1991; Bajt et al., 1990). They have since been confirmed as N-linked oligomannosidic glycans in the mammalian nervous system (Schmitz et al., 1993). Both L3 and L4 are expressed on L1 and MAG and may serve to modulate cell adhesion. The spatiotemporal expression pattern of L3 is, however, different than that reported for L2/HNK-1 suggesting that the carbohydrate epitopes on CAMs are likely to be differentially regulated and may play distinctive roles (Kucherer et al., 1987; Fahrig et al., 1990; Dennis et al., 1990). Furthermore, L3 and L4 may serve to play a role in the mediation of the *cis* interaction between L1 and NCAM within the membrane (Horstkorte et al., 1993).

CD15/Lex/L5

The cluster of differentiation (CD) 15 epitope (Lewis^x, Le^x) is a trisaccharide carbohydrate antigen consisting of an N-acetyllactosamine (Galβ1,4GlcNAc) unit with a fucose residue attached in an α1,3 linkage to the GlcNAc (Fig. 3) which was first identified by a neutrophil-specific monoclonal antibody (Feizi, 1985). It is found widespread throughout the body and is expressed on neural cell glycoproteins and glycolipids where it is developmentally regulated and has also recently been identified as the L5 epitope (Streit et al., 1996; Mai and Schonlau, 1992). Its histochemical expression pattern in the CNS, which is dissimilar to the other carbohydrate epitopes described to-date, suggests that it may play a role in cell adhesion (Feizi, 1991; Mai et al., 1995; Bartsch and Mai, 1991; Marani and Mai, 1992; Andressen and Mai 1995). The cellular expression of the epitope is cell-type specific with high levels in astrocytes and oligodendrocytes but not in neurons or microglia (Satoh and Kim, 1994). CD15 can also exist in a sialylated form (termed sialyl Le^x), which may serve to modify the adhesive function of the trisaccharide backbone during cell development (Stark and Stapper, 1992).

The Function of Glycoproteins in the Nervous System

Glycoproteins and Development

The migration and positioning of the neurons in the developing CNS is one of the central issues in neurobiology. The pattern of neuronal migration determines the cytoarchitecture in various neural structures and the subsequent specificity of their interactions. Neuronal positioning and the consequent generation of synapses is mediated primarily by two groups of proteins: the cell-adhesion molecules (CAMs) and the diffusible growth factors. CAMs serve to mediate both cell–cell interactions and cell adhesion to elements of

the extracellular matrix and these regulate the spatiotemporal regulation and stimulate adhesion-mediated neurite outgrowth and positioning. The soluble diffusible growth factors are produced in discrete areas of the CNS to act as specific guidance agents to direct the neurites to the correct regions, initially on a global scale but later at a local level. In this section, the role played by the CAMs in the developmental process will be discussed.

Integrins

The particular role of cell–substratum adhesion in CNS development was outlined in early experiments that demonstrated a good correlation between the strength of adhesion and the induction and elongation of neural processes. The pattern of fibronectin expression in the developing chick eye, for example, was found to be consistent with its proposed role in the positioning and migration of neurons during development (Kurkinen et al., 1979). Suppression of its release resulted in the blockade of focal adhesion point formation, which typically contains the protein (Virtanen et al., 1982). A second component of the ECM, laminin, is secreted by neural cells at specific stages during migration and development (Palm and Furcht, 1983). There is, however, a differential requirement for the components of the laminin and fibronectin ECM by cells in discrete CNS regions, thus providing a mechanism by which individual developing neural cells can discriminate between specific pathways and target areas (Rogers et al., 1983).

Neural cells interact with the elements of the ECM largely via members of the integrin family so these proteins would be expected to play a pivotal role in modulating developmental cues associated with cell–ECM interaction. There is a differential expression of members of the integrin family during development that is determined both by the stage of development and the particular brain region (Calof et al., 1994; Tomaselli et al., 1993; Einheber et al., 1993). Furthermore, there is some evidence for an ability of certain neuronal cells to distinguish between the individual components of the ECM during development, a property that may be related to the signaling property of the proteins (Gomez et al., 1996). Carbohydrate epitopes have also been implicated in the developmental interaction between integrins and elements of the ECM during development with the L2/HNK-1 carbohydrate demonstrated to modulate cellular binding to laminin (Hall et al., 1997).

N-Cadherin

N-cadherin has also been demonstrated to play a role in both morphogenesis and histogenesis. In the chick neuromuscular system, it is expressed on the surface of myoblasts and myotubes in the early embryonic stages where it plays a critical role in the fusion of primary myoblasts. It may also play a role in the structuring and stabilization of myelin sheaths (Cifuentes Diaz et al., 1994). Blockade of cadherin function results in an impairment of directional-associated neurite outgrowth (Honig and Rutishauser, 1996).

Other members of the cadherin family, such as M- and T-cadherin, have also been demonstrated to play a role in the neurodevelopmental process (Fredette and Ranscht, 1994; Matsunami and Takeichi, 1995; Sugimoto et al., 1996; Rose et al., 1994) and particularly in neuronal sorting and aggregation in the early stages of development (Redies and Takeichi, 1996). However, whereas each of the members of the family play a specific role, there is evidence to suggest that there may be some overlap permitting the substitution of one member of the family for another under certain circumstances (Larue et al., 1996).

Immunoglobulin Superfamily

The widespread role of members of the Ig superfamily of proteins in the developmental process has been well documented (Baldwin et al., 1996). NCAM expression is developmentally regulated and it exhibits a strict spatiotemporal pattern of expression in both neural and nonneural tissue (Baldwin et al.,

1996; Fazeli et al., 1996) with the membrane-bound form of the protein being critical for the mediation of its adhesive function (Saffell et al., 1995; Rabinowitz et al., 1996). In particular, it is expressed during the early stages of neuronal cell development prior to cell maturation (Gopinath et al., 1996). In addition, the PSA carbohydrate epitope plays a critical role in modulating the adhesive function of the NCAM backbone ensuring that its adhesivity is appropriate for the given stage of developmental (Rutishauser and Landmesser, 1996; Fryer and Hockfield, 1996). The spatiotemporal pattern of PSA expression in the spinal cord and in the olfactory system suggests that it may play a role in corticospinal axonal pathfinding prior to target recognition and innervation (Daston et al., 1996; Landmesser et al., 1990; Paz et al., 1995; Joosten et al., 1996). In NCAM knock-out mice, there is a defect in neuronal migration in the olfactotry bulb, and this is considered to be directly attributable to the loss of PSA-NCAM (Cremes et al., 1994; Ono et al., 1994; Hu et al., 1996). However, the developmental pattern of the remainder of the CNS in the NCAM knock-out mice appears to be largely normal, suggesting that the loss of one CAM can be compensated for by the other cell-surface glycoproteins.

In addition to its role in development, PSA is also reexpressed during neuronal sprouting following cell damage. Whereas this is observed primarily in the PNS, there is some evidence for a limited reexpression within the CNS. For example, following lesioning of the ipsilateral entorhinal cortex, the recipient regions of the dentate molecular layer re-express PSA-NCAM during reinnervation, with PSA expression decreasing following the reformation of synaptic connections (Styren et al., 1994). A similar expression pattern has been reported following lesioning of the sensorimotor cortex (Seele and Chesselet, 1996). PSA re-expression can be demonstrated primarily, however, in PNS regeneration and has been demonstrated, for example, in myelinated axons during repair following neuropathy induced by 2,5-hexanedione (Carratu et al., 1996). In addition, there is ample evidence for its re-expression following axonal transsection (Rutishauser and Landmesser, 1996). The adhesion properties of NCAM are partially mediated by its heparin-binding properties and these may also play a role in certain brain regions such as the developing telencephalon and diencephalon where there is a good correlation between NCAM expression and that of heparin sulfate proteoglycans (Fuxe et al., 1997).

L1 has also been demonstrated to play a role in both neural development and regeneration and its expression is controlled, at least in part, by cell–cell contact (Kobayashi et al., 1992). L1 is expressed to a high level in the granule and molecular layers and in the Purkinje cell layer of the cerebellum during the fetal period and continuing into early infancy, suggestive of a role in the mediation of cell migration, neurite elongation, and axonal fasciculation (Tsuru et al., 1996). L1 may also play a role as an anatomical template for developing retinal ganglion axons as they penetrate the ventral diencephalon (Sretavan et al., 1994). In the hippocampus following lesioning of the ipsilateral entorhinal cortex, L1 staining corresponds with fiber outgrowth with an axonal localization. This staining pattern was distinct, however, from that observed for NCAM suggesting that the two proteins have distinctive roles in the process of neurite outgrowth, both during development and regeneration (Styren et al., 1995). In the PNS, L1 exhibits a distinct spatiotemporal expression during the development of dorsal root ganglia (Moscoso and Sanes, 1995) and in sensory neurons, its expression can be upregulated by neural impulse activity, one of the factors proposed to play a role in neuronal development (Itoh et al., 1995).

The other members of the Ig superfamily also play a distinct role in the modulation of the developmental process. The myelin-associated glycoprotein, P_0, is expressed at a high level during the early stages of peripheral neuronal

myelination with a sharp decrease in levels following nerve maturation, indicating its role in the myelination process (Baron et al., 1994). However, MAG, another component of myelin, may play a role in the maintenance rather than the development of the PNS myelin sheath as MAG-deficient mice develop normal myelin sheaths but show disturbances in its maintenance during adulthood (Fruttiger et al., 1995). In the CNS of these animals, however, there was a delay in the onset of oligodendrocyte-associated myelination resulting in subtle morphological abnormalities (Montag et al., 1994). Another protein that may play a role in the development and maintenance of synaptic contacts in the postnatal rather that the embryonic brain is the F3 protein that is expressed primarily following birth with levels peaking in adulthood and is localized at synaptic contact sites (Hosoya et al., 1995; Faivre Sarrailh et al., 1992). In contrast, TAG-1/axonin-1 is expressed primarily in the embryo where it plays a role in axonal guidance and migration (Stoeckli and Landmesser, 1995; Wolfer et al., 1994).

Whereas the individual CAMs each play a specific role in development and they exhibit unique expression patterns in particular brain regions, there may also be a certain functional cooperation between the individual proteins. L1 and axonin-1 are present in growth cones where their distribution pattern is suggestive of a functional cooperation between the two proteins (Stoeckli et al., 1996). In the regenerating optic nerve, NCAM, L1, and MAG are all present on the cell surface of the regenerating axon, suggesting that they are involved in the cell-adhesion events associated with the regenerative process (Dezawa and Nagano, 1996). A similar L1/NCAM expression pattern has been observed in the developing olfactory nerve (Gong and Shipley, 1996) and, in developing Schwann cells, the expression of both NCAM and L1 is upregulated in response to the transforming growth factor-β (TGF-β) (Stewart et al., 1995). In contrast, however, the expression of the P_0 and MAG proteins in Schwann cells is inhibited by TGF-β illustrating the differential roles in development of the members of the Ig superfamily in particular developmental phases (Guenard et al., 1995).

Amyloid β Precursor Protein

AβPP, as a multifunctional protein, has the potential to influence the developmental process at a number of levels. As a cell-adhesion molecule, it mediates cell–cell and cell–ECM interaction, as well as adhesion-mediated neurite outgrowth. However, the soluble form of the protein has also been demonstrated to exhibit neurotrophic actions. Several studies have indicated that in the developing brain, AβPP can play a role in regulating neurite process outgrowth and synaptogenesis. In the early stages of development in the chick brain, the level of AβPP increases between embryonic d 6 and 9, coincident with neurite outgrowth (Small et al., 1992). This increase in AβPP during the early stages of neural development is not species-specific and has been observed in the human (Arai et al., 1994), mouse (Salbaum and Ruddel, 1994), hamster (Moya et al., 1994), and rat (Ohta et al., 1993) CNS. AβPP expression continues to increase during the later stage of neural differentiation coincident with early synaptogenesis (Hung et al., 1992; Konig et al., 1992) and peaks in the second postnatal week (Sherman and Higgins, 1992) after which it decreases to adult levels (Moya et al., 1994) where it may play a role in synaptic maintenance (Schubert, 1991; Doyle et al., 1990; Shivers et al., 1988). During the early stages of development, AβPP expression is regulated by neurotrophic factors such as the nerve-growth factor (NGF; Refolo et al., 1989; Clarris et al., 1994; Cosgaya et al., 1996). This interaction may, however, be a complex one as AβPP can also act to mediate the effect of NGF on neuronal outgrowth (Milward et al., 1992). The expression of the chondroitin sulfate forms of both AβPP and APLP-2 are also developmentally regulated increasing with age, suggesting a role for this form of the protein in axonal sprouting and neurite outgrowth (Crain et al., 1996).

The Role of Glycoproteins in Synaptic Plasticity

Because of their pivotal role in the control of synaptogenesis during development, cell-surface glycoproteins also play a key role in the process of synaptic plasticity and the CNS functional modifications that are associated with memory acquisition, such as information storage, require *de novo* synapse formation and/or modification of existing synapses (Bailey and Kandel, 1993). Early studies demonstrated that memory training resulted in an increase in CNS protein glycosylation, thus providing initial evidence that glycoproteins in general, and the protein glycosylation state in particular, may play a key role in the cellular events underlying memory acquisition (Popov et al., 1980; Bourne et al., 1991). The potential role of individual sugar residues was underlined by studies carried out using 2-deoxygalactose (2-dgal), which acts as an inhibitor of terminal fucosylation and which, if injected at specific time points prior to, or following training, impaired the acquisition of a memory paradigm (Rose and Jork, 1987; Scholey et al., 1993). The potential role of glycosylation in general, and fucose in particular, was underlined by experiments that demonstrated an increase in cellular fucose uptake following the induction of long-term potentiation (LTP), an electrophysiological paradigm of plasticity (Angenstein et al., 1992), and that pretreatment of animals with fucose or 2-fucosyllactose served to enhance certain aspects of LTP (Krug et al., 1994). LTP could also be inhibited by 2-dgal pretreatment (Krug et al., 1991). This learning-associated increase in fucose uptake however, occurs, independently of the biosynthesis of the protein backbone (McCabe and Rose, 1987).

The general role of glycoproteins in plasticity has been underlined by studies demonstrating an improvement in learning ability following the pretreatment of animals with corticosteroids prior to the acquisition of the memory paradigm (Sandi et al., 1995; Sandi and Rose, 1994). Whereas the molecular mechanisms underlying this have not been identified, corticosteroids have been demonstrated to increase the rate of glycoprotein biosynthesis in general and of NCAM and L1 in particular (Sandi et al., 1995; Grant et al., 1996). In addition, corticosteroids can influence the activities of the ST enzymes (*see* N-Linked Biosynthesis), with a consequent change in the protein sialylation state (Coughlan et al., 1996a, b).

In addition to general changes in protein glycosylation associated with synaptic plasticity, studies have been carried out to delineate the exact roles of individual cell surface glycoproteins in the memory and learning processes. The role of NCAM has been studied using a number of complementary model systems. Initial studies demonstrated that an intraventricular infusion of anti-NCAM antisera inhibited the acquisition of a passive avoidance memory paradigm in both the rat (Doyle et al., 1992) and the chick (Scholey et al., 1993). This effect was, however, time dependent with the effect being observed if the antibody was injected at 6 h posttraining, but not if injected just prior to the training period, thus suggesting that memory acquisition consists of a number of discreet phases with NCAM playing a role in the later stages of memory consolidation. Subsequent studies have confirmed the role of NCAM in plastic events using other behavioral paradigms (Arami et al., 1996). Furthermore, NCAM-deficient mice demonstrated a significant decrease in the size of the olfactory bulb, an area that exhibits ongoing synaptic rearrangement throughout adulthood (Cremer et al., 1994). These animals, however, only exhibit a minor deficit in learning ability with a decrease in spatial learning, but no change in activity or motor ability, suggesting that no single glycoprotein is essential for synaptic plasticity, but rather that the complement of cell surface proteins probably act in tandem to modulate synapse formation. If one protein is missing, particularly from the early stages of development, the cells appear to have the ability to adapt for the loss of this protein by the use the other CAMs (Cremes et al., 1994).

In addition to the role of the core glycoprotein, the expression of the PSA group of NCAM serves to further modulate cell–cell interaction during synaptic reorganization. Following the acquisition of a one-trial passive avoidance memory test or multitrial spatial learning, the number of polysialylated neurons in the dentate gyrus of the hippocampus undergoes a rapid and transient increase after 4–12 h of the task (Fox et al., 1995; Murphy et al., 1996). These changes in the PSA-NCAM staining pattern after training were confirmed by an immunoelectron microscopic study (Rusakov et al., 1994). Whereas LTP is accepted to mimic certain events associated with synaptic reorganization and plasticity, recent results suggest that it may not mimic the specific events underlying spatial learning (Nosten-Bertrand et al., 1996). The induction of LTP in hippocampal slices was associated with an increase in PSA expression and subsequent treatment with endoneuraminidase-N to remove the PSA resulted in an inhibition of the maintenance phase of LTP without any effect on the NMDA receptor-associated component (Becker et al., 1996; Muller et al., 1996). Furthermore, the intraventricular infusion of anti-NCAM antibodies and peptides served to inhibit LTP induction (Lüthl et al., 1994; Ronn et al., 1995). The control of PSA expression may also have an activity-related component as its induction is blocked by the addition of tetrodotoxin and enhanced by bicucculine. PSA-NCAM expression can also be stimulated in O-2A glial precursor cells following activation of NMDA receptors (Wang et al., 1996). Once appropriate contacts have been made, then the PSA is down-regulated to allow the NCAM homophilic binding associated with synaptogenesis. Further evidence for the role of NCAM in LTP maintenance has been provided by the demonstration of a precise temporal release of NCAM fragments from the hippocampus following LTP induction (Fazeli et al., 1994). The fact that protease inhibitors can interfere with LTP suggests that during the early phases, there may be a cleavage of certain cell-surface glycoproteins, including NCAM, prior to synaptic reorganization. In addition to its role in the hippocampus, PSA-NCAM has been demonstrated to be involved in the processing of auditory activity in the inner ear (Kajikawa et al., 1997). The persistence of PSA results in inappropriate synaptic structuring as is seen in the cerebellum of the stagger mouse (sg/sg), in which there are functional deficits (Edelman and Chuong, 1982).

Aging animals have been demonstrated to have a decrease in general learning ability, probably associated with a decrease in synaptic plastic potential. Whereas older animals exhibit a decrease in PSA-NCAM expression levels (Fox et al., 1995), there is no apparent correlation between the age-related decrease in cognitive ability and changes in PSA-NCAM expression suggesting that the two parameters may not be related and that other factors may play a role in the effects of aging on CNS function (Abrous et al., 1997).

The expression of PSA-NCAM has also been reported in those areas of the mature brain that continue to undergo structural rearrangement. In the hippocampal dentate gyrus, an area that is found deep within the granule cell layer, neuronal cells are continually being generated and this developing area stains strongly for PSA expression (Bonfanti et al., 1992). Neurons that migrate towards the olfactory bulb are also continually formed throughout adult life. In NCAM-null transgenic mice, or if PSA has been chemically cleaved by endoneuraminidase, then the migration of these cells is impaired with a consequent reduction in the size of the olfactory bulb (Cremer et al., 1994). However, this trend does not occur indiscriminately over the CNS. Taste receptor cells and their nerve fibers are also replaced throughout life although they do not express PSA-NCAM during regeneration (Smith et al., 1994).

L1 has also been associated with synaptic plasticity. A continuous intraventricular infusion of anti-L1 antibodies or fragments of the extracellular domain of the protein resulted in the inhibition of spatial learning in the rat (Arami et al., 1996; Rose, 1995). The precise regulation of glycoprotein expression is, however,

pivotal for plasticity and an overexpression of L1 can also serve to impair the induction of LTP (Luthi et al., 1996). Thy-1 has also been demonstrated to play a role in the maintenance of LTP and there is a significant impairment of LTP in Thy-1-deficient mice. These animals perform normally in spatial learning paradigms suggesting that individual adhesion molecules may modulate specific aspects of synaptic plasticity (Nosten-Bertrand, 1996).

In a similar fashion to L1 and NCAM, an intraventricular infusion of antibodies to AβPP serves to impair the acquisition of a passive-avoidance paradigm (Doyle et al., 1990) and the protein has also been implicated in the regulation of synaptic function in *Drosophila* (Kim et al., 1995). Furthermore, the precise temporal release of proteolytic fragments of AβPP following the induction of LTP suggests that its cleavage at the level of the cell membrane may be a prerequisite for synaptic reorganization and the use of protease enzyme inhibitors will impair LTP induction (Fazeli et al., 1994).

Glycoproteins as Targets for Neurotoxin Action

The development of the nervous system in general, and the CNS in particular, is a complex event that is heavily reliant on the correct spatiotemporal arrangement of the constituent neural cells at specific developmental stages which in turn is controlled by the expression of key cell-surface glycoproteins. An early developmental event in human CNS development is the formation of the neural tube at 21–26 d after conception, which is coincident with the formation of the first neurons. By the second trimester of pregnancy, the glial cells have appeared and serve as insulators to promote the efficient conduction of electrical signals by neuronal cells. From 6 wk *in utero,* until 5 m after birth in the human, the neuronal cells migrate from the neural tube to form the central regions of the CNS and, although the visual connections are completed by 3–4 yr of age, the brain still continues to form other connections until about the age of 20 yr, at which point it is considered a mature structure. At each of these stages of development, correct cell–cell interaction is critical and both surface and extracellular glycoproteins play a key role in ensuring the accurate positioning of the cells. Because of the complexity of these developmental events, the immature CNS is particularly sensitive to the actions of toxic agents (Reuhl et al., 1994). Examples of teratogenic agents that target the developing nervous system include chronic low-level lead (Lansdown and Yule, 1986), solvents (Kentroti et al., 1995), insecticides, polyhalogenated hydrocarbons, and psychoactive drugs taken by the mother (Slikker, 1994). However, once the mature CNS has been formed and all of the cells are stabilized, there are no more "critical windows" and it thus becomes less vulnerable to the actions of neurotoxins. Therefore, whereas the mature CNS may also provide a target, the many developmental processes make the immature CNS a much greater target for the actions of neurotoxins.

The Actions of Teratogenic Neurotoxins

Whereas low-level lead exposure during the early stages of development does not produce gross clinical symptoms of toxicity such as encephalopathy, children with a raised blood-lead level appear to score lower on standard IQ tests than their nonaffected peers as a result of some subtle CNS damage (Winneke, 1995). Although the majority of studies in this area have been epidemiological, some animal models have also been employed to further investigate the cellular alterations that occur after chronic low-level lead exposure.

Animals that have been subjected to chronic low-level lead exposure, either from the time of conception or from birth, experience recall deficits after passive avoidance training (Regan and Keegan, 1990), with no apparent gross CNS anatomical abnormalities. This suggests that the cognitive deficits may arise from

subtle dysfunctions at the level of the individual synapse. Whereas studies have demonstrated changes in the expression and function of glutamatergic and cholinergic neurotransmitter receptors following lead exposure (Cory Slechta, 1995; Jett and Guilarte, 1995), proteins that play a role in cytoarchitectural development also provide a target for the actions of the teratogen (Zawia and Harry, 1996).

As NCAM plays a pivotal role in the regulation of synaptogenesis, it was investigated as a potential target for lead's actions. Chronic low-level lead exposure can impair the developmental desialylation of NCAM at a period coincident with synapse formation (Cookman et al., 1987) and this may be caused by an interaction between lead and the controlling sialyltransferase enzyme (Breen and Regan, 1988; Hayes and Breen, 1994). In the adult brain, the expression of PSA-NCAM can be further upregulated after a learning task. Whereas there was no increase in the relative density of PSA-NCAM-staining neurons in the dentate area of animals following chronic perinatal exposure to low-level lead, the area was enlarged by 20% after 40 d lead treatment, giving rise to an increased number of PSA-NCAM neurons in absolute terms (Murphy et al., 1995). This increase suggests that the lead may be interfering with the early neuronal structuring with a subsequent impairment of the full neuroplastic potential of the young adult because of the earlier structural abnormalities. In addition to NCAM, N-cadherin may also provide a target for the actions of low-level lead. The binding of N-cadherin is calcium-dependent and any agents that act to compete for the calcium-binding sites of the protein, such as lead, may interfere with the protein binding with consequent upsets in neuronal patterning (Lagunowich et al., 1994).

Chronic perinatal ethanol administration also displays neuroteratogenic effects including a decrease in the rate of both neuronal survival and neurite outgrowth, resulting in mental retardation, hydrocephalus, and agenesis of the corpus callosum with consequent behavioral deficits during postnatal development (Heaton et al., 1994; Heaton and Bradley, 1995). Studies using chick embryos demonstrated an increase in PSA-NCAM expression at embryonic d 8 following ethanol treatment at embryonic d 1–3. Similar changes in NCAM expression were observed in vitro using neuroblast-enriched cultures derived from 3-d-old whole chick embryos with profound alterations in neuronal growth patterns (Kentroti et al., 1995). The changes in NCAM expression levels may be mediated by an ethanol-associated inhibition of the recombinant human osteogenic protein-1 (hOP-1), which stimulates the expression of NCAM and L1 and therefore the strength of cellular adhesion (Charness et al., 1994), or may be a direct result of an interaction between ethanol and the cellular glycosylation pathway (Ghosh and Lakshman, 1997). The effects of ethanol on L1 have been confirmed by in vitro studies that demonstrated that chronic ethanol treatment resulted in a complete inhibition of L1-mediated adhesion in both L1-transfected fibroblasts and NIH/3T3 cells with a similar effect being also observed with propanol and butanol (Ramanathan et al., 1996). Because of the role of the *cis* interaction between L1 and NCAM within the membrane in the modulation of L1-mediated adhesion, it is possible that agents, such as ethanol, which influence membrane fluidity may act, at least in part, to interfere with this protein–protein interaction. Ethanol also acts to modulate some of the actions of growth factors and potentiates NGF-induced expression of Thy-1 (Messing et al., 1991). Because of its role in the modulation of adhesion-dependent neurite outgrowth (Doherty et al., 1993), an upset in its expression may result in an upset in developmental patterning.

Perinatal exposure to methanol, which may occur because of its increasing use in motor fuel, also results in CNS deficits and an analysis of the brains of rats exposed to low-level methanol vapor for 6 h/d throughout pregnancy showed a decrease in total NCAM staining in pups at postnatal d 4 (Stern et al., 1996).

The Effects of Chronic Toxin Treatment

Acute trimethyltin treatment results in memory and learning deficits in the adult (Earley et al., 1992). Although the molecular mechanisms underlying these changes are unclear, recent studies have proposed NCAM expression as a possible target. As early as 4 h after toxin administration, there was a selective decrease in the expression of $NCAM_{180}$ in the hippocampus and cerebellum in TMT-treated rats, with the maximum effect at 8 h and recovery after 64 h. As $NCAM_{180}$ is involved in synaptic stabilization through an interaction with the cytoskeleton, a loss of this isoform may serve to destabilize synaptic connections with a resulting upset in behavior (Dey et al., 1994). TMT acts to increase intracellular free calcium (Komulainen and Bondy, 1987), and this may serve to activate calcium-dependent proteases, such as calpain I, with an increased rate of NCAM proteolytic breakdown (Covault et al., 1991).

The Role of Glycoproteins in Disease

Glycoprotein Mutations

L1 mutations have been implicated in a number of neurodevelopmental disorders including X-linked hydrocephalus (Kenwrick et al., 1986; Van Camp et al., 1993), MASA (mental retardation, aphasias, shuffling gait, adducted thumbs) syndrome (Jouet et al., 1994), complicated X-linked spastic paraplegia (SP-1), X-linked mental retardation-clasped thumb (MR-CT) syndrome, CRASH syndrome (clinical spectrum of corpus callosum hypoplasia, retardation, adducted thumbs, spastic paraparesis, and hydrocephalus), and some forms of X-linked agenesis of the corpus callosum (ACC) (Franien et al., 1996). Analysis of the mutations associated with these disorders has demonstrated that they serve primarily to change the conformation of the protein or to denature the specific domain, thus interfering with the adhesive potential of the protein (Bateman et al., 1996).

P_o is an adhesive glycoprotein associated with peripheral myelin and point mutations in the P_o gene have been associated with several inherited neuropathies including Charcot-Marie-Tooth (CMT) disease type 1B and Dejerine-Sottas (DS) disease (Vyemura et al., 1994; Gabreels Festen et al., 1996). In addition, children with severe hypertrophic peripheral neuropathy (Ben Jelloun Dellagi et al., 1992) as well as patients with IgM gammopathy and polyneuropathy (Bollensen et al., 1988) have been demonstrated to express antibodies directed against P_0. Similar abnormalities have been observed in P_0-deficient mice (Zielasek et al., 1996).

MAG can also provide a target for peripheral neuropathies and in the benign monoclonal gammopathies of undetermined significance (MGUS), monoclonal antibodies are generated that are directed against certain carbohydrate epitopes present on MAG and can interfere with cell adhesion and the cellular-signaling process and thus modify axon-Schwann cell interaction (Mieschner and Steck, 1996). In the quaking mouse model of dysmyelination, there is a change in the MAG glycosylation pattern with an increase in α2,3-linked sialic acid as well as increased oligosaccharide branching with a concomitant decrease in L2/HNK-1 (Bartoszewicz et al., 1995).

Carbohydrate-Deficient Glycoprotein Syndrome

Carbohydrate-deficient glycoprotein syndrome (CDG) is a group of recessively inherited metabolic disorders characterized by neurological and developmental defects resulting in CNS dysfunction with associated cerebellar hypoplasia, supratentorial atrophy, polyneuropathy, growth retardation and stroke-like episodes (Jensen et al., 1995; Akabashi et al., 1995). The disease is caused by a deficiency in the activity of the Golgi enzyme β1,2-*N*-acetylglucosaminyltransferase II (GnT II), which transfers GlcNAc onto the α1,6-linked mannose residue in the core of complex N-linked oligosaccharides (Fig. 2; Jaeken et al.,

1994), and recently two unrelated CDG patients were demonstrated to have point mutations in the catalytic domain of this enzyme (Tan et al., 1996). An animal model lacking the GnT I enzyme, which transfers GlcNAc onto the α1,3-linked core mannose residue, has also been demonstrated to exhibit severe developmental defects with the majority of animals not surviving past the mid-stage of gestation (Ioffe and Stanley, 1994). These findings outline the critical role of mature N-linked carbohydrates for correct neural development.

Amyotrophic Lateral Sclerosis

Neurodegenerative diseases in humans are progressive and fatal and there are very few effective treatments. Some neurodegenerative conditions have a purely genetic etiology (e.g., Huntington's disease), others are not hereditary (e.g., Parkinson's disease), and yet others have subtypes that are both genetically determined and of unknown aetiology (e.g., Alzheimer's disease and amyotrophic lateral sclerosis, ALS). Neurodegenerative diseases generally display a unique neuropathology and recent studies have suggested that changes in the expression and posttranslational modifications of certain key glycoproteins may play a pivotal role in the onset of the diseases.

ALS is a chronic, progressive, degenerative process involving both the cortico-bulbospinal and lower motor neurons, leading to a mixture of spastic and atrophic phenomena in cranial and spinal musculature. It usually begins between 40–70 yr of age, and is 3–4 times more common in men than women. The etiologies of the more common nongenetic form are unknown. A primary pathological lesion associated with ALS is an alteration in neurofilament (NF) expression with the deposition of NF-rich inclusions in spinal motor neurons (Tu et al., 1996). The potential role for NFs in the pathogenesis of ALS is further strengthened by the findings that the disease pathology can be partially reproduced in transgenic animals overexpressing the gene coding for NF-H (Lee and Cleveland, 1996; Julien et al., 1995). This upset in NF expression is thought to lead to an impairment of fast axonal transport, which is responsible for the movement of glycoproteins from the cell body to the synaptic terminal (Sasaki and Iwata, 1996).

NF are the neuronal-specific intermediate filaments that are assembled from three constituent polypeptides of apparent molecular weights of 68 kDa (NF-L), 145 kDa (NF-M), and 200 kDa (NF-H; Lee and Cleveland, 1996). They are postulated to play a role in neuronal structuring and in the determination of axonal caliber (Lee and Cleveland, 1996). In the mature axon, there is a precise stoichiometric ratio between the constituent NF components and an upset in this ratio results in the aggregation of NF within the cell body (StraubeWest et al., 1996). In addition, all three NFs are phosphorylated, with the phosphorylation levels being developmentally and spatially regulated coincident with a change in protein function (Gotow and Tanaka, 1994; Fischer and Shea, 1991). In the perikarya and developing axons, NF-H is in a relatively unphosphorylated form, whereas in mature axons, it is highly phosphorylated and it is thought that the phosphorylation of the intermediate filament cross-bridges is important in the maintenance of axonal caliber and in axonal transport.

The NF protein deposited in ALS has been reported to express altered phosphorylation (Gaytangarcia et al., 1996; Strong et al., 1995) and this change in phosphorylation state is accompanied by upsets in NF protein and mRNA expression (Bergeron et al., 1994). Activation of various cellular protein kinases, including protein kinase C, induces NF fragmentation and deposition, similar to that seen in ALS pathology (Doroudchi and Durham, 1996).

In addition to being phosphorylated, NF proteins have also been demonstrated to be *O*-glycosylated with the *N*-acetylglucosamine (GlcNAc) sugar linked to serine or threonine residues within the carboxyl-terminal triplet repeat region, which is also the region that is phosphorylated (Dong et al., 1993; Goedert et

al., 1996; Ding and Vandre, 1996). This leads to the hypothesis that changes in NF glycosylation may play a role in the development of ALS. As the same serine and/or threonine residues can be modified by either *O*-linked glycosylation or phosphorylation, it is possible that there may be a homeostatic mechanism between the two processes, i.e., if NF-H is heavily phosphorylated, there will low levels of glycosylation and *vice versa* (Hart et al., 1996). It is tempting to speculate that a potential upset in NF-H glycosylation, possibly caused by a disruption in the activity of the *O*-GlcNAc transferase enzyme, may decrease the glycosylation of the protein with a parallel increase in its phosphorylation, thereby contributing to the abnormal deposits characteristic of ALS (Hart, 1997; Hart et al., 1995).

Alzheimer's Disease

AβPP can be acted upon by the β and γ secretase enzymes to generate the 40–42-amino-acid Aβ peptide (Fig. 6) which, under certain conditions, will coalesce to generate the neurotoxic amyloid deposits that are present in the neuritic plaques of patients with Alzheimer's disease (AD). Whereas the factors controlling an increase in Aβ generation in AD are unclear, it is possible that the protein glycosylation state may influence its processing.

Mutation of the N-linked glycosylation sites of AβPP (Yazaki et al., 1996) or treatment of cells with tunicamycin (Tienari et al., 1996), the Golgi inhibitors monensin or brefeldin A (Caporaso et al., 1992) or the expression of the protein in glycosylation-defective mutant CHO cells (Pahlsson and Spitalnik, 1996) prevents AβPP maturation and decreases protein secretion. The subcellular distribution of AβPP in neuronal cells has been demonstrated to be polarized and following synthesis in the cell body, the protein is initially delivered to the axon, and later delivered to the dendrites by a transcytotic mechanism. Whereas this directional processing of the protein may also be, at least in part, a glycosylation-dependent process (Tienari et al., 1996; Hartmann et al., 1996; Simons et al., 1995), some reports suggest that the glycosylation state of other cellular glycoproteins may also be important in controlling AβPP processing (Pahlsson and Spitalnik, 1996). Furthermore, glycosylation enhances the trypsin-inhibitory function of the KPI domain-containing forms of the protein (Godfroid and Octave, 1990). AβPP also contains O-linked oligosaccharides and has been the first membrane-bound or secreted protein to express O-linked *N*-acetylglucosamine (GlcNAc), which was previously only identified on nuclear and cytoskeletal proteins (Griffith et al., 1995).

There is some evidence for an upset in the glycosylation process associated with AD that may ultimately influence the processing of AβPP and the associated generation of the Aβ peptide. There is a decrease in the activity of individual sialyltransferase enzymes in postmortem brain and serum samples from AD patients when compared with age- and sex-matched controls (Maguire and Breen, 1995; Maguire et al., 1994) that is accompanied by a change in the pattern of general protein glycosylation (Gillian and Breen, 1995). As there is some evidence that sialic acid plays a role in the processing of AβPP for secretion with $AβPP_s$ being more heavily sialylated than the membrane-bound form (McFarlane and Breen, unpublished results), a decrease in cellular ST activity may decrease the generation of $AβPP_s$, leaving a greater proportion of the protein within the membrane for potential amyloidogenic processing (Breen and McFarlane, 1996).

Studies have also been carried out on the expression of other cell-surface glycoproteins in AD. Associated with general aging, there is a slight downregulation of $NCAM_{180}$ levels that may be indicative of an age-related synapse loss (Linnemann et al., 1993). In AD, however, there is no change in NCAM expression when compared with age-matched controls (Gillian et al., 1994). In particular, there is no evidence of a re-expression of PSA-NCAM, which would be indicative of some regenerative sprouting. Furthermore, there are no changes in the expression levels of the L1 gly-

coprotein or the L2/HNK-1 carbohydrate epitope in AD (Breen et al., 1998a). Taken together, these results suggest that despite significant neurodegeneration, there is no change in the expression of the agents modulating cell–cell adhesion in AD, which is suggestive of the lack of any adhesion-stimulated neurite outgrowth.

The second characteristic pathological lesion associated with AD is the neurofibrillary tangle that is composed of an abnormally phosphorylated form of the microtubule-associated protein, tau, assembled into insoluble, paired helical filaments (PHF) which are deposited within neuronal cells prior to cell death (Alonso et al., 1996). Tau is a phosphoprotein that is composed of a number of developmentally regulated isomeric forms that are abnormally phosphorylated in the PHF (termed PHF-tau) (Lee, 1995). Many studies have been carried out in order to identify the kinase enzymes that may be responsible for the abnormal phosphorylation of tau, and while a number of potential candidate enzymes have been proposed, the specific enzyme remains to be identified.

Recent studies have, however, identified other posttranslational modifications of the tau protein that may influence its phosphorylation state and its subsequent assembly into PHF in AD. Tau is another cytoskeletal protein (like NFH) that has been demonstrated to contain a number of O-linked *N*-acetylglucosamine (GlcNAc) residues (Arnold et al., 1996) that are transferred by a GlcNAc-transferase enzyme that may be cytosolically located (Hart et al., 1996). The GlcNAc moiety is attached in an O-linkage to serine or threonine residues of the protein. However, these residues are also those that are phosphorylated, thus suggesting an interaction between O-GlcNAcylation and phosphorylation of tau (Hart, 1997). Because tau is abnormally phosphorylated in AD, it is tempting to speculate that an upset in the glycosylation process may play a role in influencing the altered protein phosphorylation state. Indeed, recent reports suggest that there may be an upregulation in cytoskeletal-associated O-linked GlcNAc residues in AD brain samples, which would further support a role for altered glycosylation in PHF-tau formation (Griffith and Schmitz, 1995). Finally, protein glycosylation may play a role in the assembly of tau into PHF in AD as recent reports have suggested that heparin-sulfate proteoglycans may stimulate PHF assembly (Goedert et al., 1996), and the tau glycosylation state may influence its interaction with HSPGs.

Schizophrenia

Whereas schizophrenia is a relatively common disorder affecting up to 8 per 1000 people, the pathogenesis of this disease and other mood disorders is unknown. One theory of the disease is termed the neurodevelopmental hypothesis that suggests that a disruption of brain development *in utero* may alter CNS structure and function with the appearance of symptoms decades later upon maturation of the brain (Waddington, 1993). A number of cytoarchitectural abnormalities have been described in various regions of schizophrenic brains including the medial temporal lobe (Roberts, 1991), the hippocampus (Conrad et al., 1991), the entorhinal cortex (Arnold et al., 1991), and the prefrontal and cingulate cortices (Benes et al., 1991). Because of its pivotal role in development, the expression of NCAM has been investigated in schizophrenia. There is a significant decrease in hippocampal PSA-NCAM staining in the schizophrenic brains when compared with controls, without any overall changes in NCAM protein levels (Barbeau et al., 1995). In addition, there is evidence for an upset in the ST activity control mechanisms in schizophrenic patients which may account for the changes in PSA expression levels (Maguire et al., 1997). The change in PSA-NCAM expression is suggestive of an altered neuronal plasticity which provides a basis for some of the behavioral symptoms associated with the disease. More recent studies have also demonstrated an increase in CSF levels of NCAM but a decrease in L1 in patients with schizophrenia or mood disorder (Poltorak et al., 1995, 1996) and as previous studies have

suggested that alterations in CSF levels of neural proteins may mirror changes that occur within the CNS, the changes observed in CSF NCAM and L1 levels may reflect an altered synaptic plastic potential within the CNS.

Prion Diseases

The prion diseases or transmissible spongiform encephalopathies, including bovine spongiform encephalopathy (BSE) in cattle and Creutzfeldt-Jakob disease (CJD) in humans, are associated with an abnormal form of the host prion glycoprotein (PrP^{c}) that is insoluble and resistant to protease action (PrP^{Sc}). Although the exact events associated with PrP^{Sc} generation transmission remain uncertain, the available evidence (The Prion Hypothesis) suggests that PrP^{Sc} is derived from PrP^{c} by a posttranslational mechanism involving the interaction between the two forms of the protein resulting in a conformational change of the PrP^{c} to the PrP^{Sc} form (Prusiner, 1996). PrP^{c} is a 33 kDa GPI-linked sialoglycoprotein associated with cholesterol-rich domains within the membrane that can be cleaved to release a soluble protein (Perini et al., 1996; Taraboulos et al., 1995). PrP^{c} can also bind to heparin sulfate proteoglycans and may play a role in cell adhesion (Gabizon et al., 1993). Glycosylation is important for PrP^{c} processing and under normal circumstances, deglycosylated forms of the protein do not tend to reach the cell surface (Petersen et al., 1996)

Perhaps the most important aspect of the prion diseases is their transmissibility and particularly their ability to cross species barriers. This has been highlighted in the UK recently with some evidence for the potential transmission of the bovine form of the disease (BSE) to humans to result in the development of CJD. Whereas original studies suggested that BSE could not be passed to humans, this recent development is thought to have arisen through to the development of a new strain of BSE with altered characteristics permitting it to cross the species barrier. Within humans, different strains of CJD have been identified which differ in both the size and glycosylation pattern of the PrP^{Sc} protein (Parchi et al., 1996). The strain of CJD, which may have been transmitted from cattle to humans, has been termed "new variant" CJD as it exhibits different properties to the strains of CJD already characterized and resembles those of BSE. In addition to its protein-banding patterns, the new variant CJD also exhibits different glycosylation patterns similar to those observed in BSE (Collinge et al., 1996). Although further studies in this area are required, protein glycosylation may be a key factor in differentiating between the individual PrP^{Sc} strains and their ability to interact with the endogenous PrP^{c} in different species.

Outlook

Whereas protein glycosylation plays a significant role in nervous system function, this is an area of neurobiology which has only recently come to the fore. Although its role in cell adhesion, in particular, has been well characterized, we are only now coming to understand the factors controlling protein glycosylation and how these may be influenced, both within the CNS, and by external factors such as pharmacological agents. In addition, whereas the majority of the neurotransmitter receptors are glycoproteins, this additional mechanism whereby their function could be modulated has attracted relatively little attention. Future studies in this area may provide a greater insight into the control of receptor function and thus serve to generate a novel and exciting therapeutic target.

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