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ORIGINAL ARTICLE

Conformations of peptides derived from myelin-specific proteins in membrane-mimetic conditions probed by synchrotron radiation CD spectroscopy

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Abstract Myelin is a tightly packed membrane multilayer in the nervous system, which harbours a specific set of quantitatively major proteins. All these proteins interact with the lipid bilayer, being either peripheral or integral membrane proteins. In this study, we examined the conformational properties of peptides from the myelin proteins P0, CNPase, MOBP, P2 and MOG, using trifluoroethanol and micelles of different detergents as membrane-like mimics. The peptides showed significant differences in their folding under the employed conditions, as evidenced by synchrotron radiation circular dichroism spectroscopy. Our experiments provide new structural information on the interactions between myelin proteins and membranes, using a simplified model system of synthetic peptides and micelles.

Keywords Myelin · Peptide · Synchrotron radiation · Folding · Micelle

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Introduction

The rapid transmission of nerve impulses is a strict prerequisite for the normal functioning of the vertebrate nervous system. This saltatory conduction is enabled by the presence of myelin, a multilayered structure formed of lipid bilayers and specific proteins. Myelin-specific proteins are mostly integral or peripheral membrane proteins, and it is likely that their correct interactions with the lipid membrane are important for myelin structure and function. While their ultrastructures are similar, the myelin sheaths in the central (CNS) and peripheral (PNS) nervous systems differ biochemically.

The myelin protein, for which most studies on membrane binding have been carried out, is myelin basic protein (MBP). It is an unfolded protein in aqueous solution, but obtains significant amounts of secondary structure when interacting with membrane mimics, such as detergent micelles and trifluoroethanol (TFE) (Libich and Harauz 2008; Majava et al. 2010b). Detergents have been used as membrane-mimicking conditions for MBP, especially dodecylphosphocholine (DPC) (Libich and Harauz 2008, Bamm et al. 2010). Little data are available for several of the other myelin-specific proteins with respect to details of membrane surface binding.

Myelin protein zero (P0) is a quantitatively major protein in PNS myelin (Greenfield et al. 1973), which has a single extracellular immunoglobulin domain, a single transmembrane domain and a short cytoplasmic tail with no homology to other proteins. It is believed to be adhesive between successive turns of the myelin membrane, on both the extracellular and the intracellular side (Eichberg 2002). A Cys residue at the beginning of its cytoplasmic domain is known to be acylated (Bizzozero et al. 1994), and quite likely represents an additional membrane-association site.

The myelin-associated oligodendrocytic basic protein (MOBP) is a poorly characterized component of the CNS myelin sheath (Yamamoto et al. 1994), which is one of the main autoantigens of multiple sclerosis (de Rosbo et al. 2004; Montague et al. 2006; Kaushansky et al. 2010). It has a number of splice isoforms (Kaushansky et al. 2010), and based on sequence analysis, harbors a FYVE zinc finger domain at its N-terminus (Kursula 2008).

The myelin/oligodendrocyte glycoprotein (MOG) is structurally homologous to P0 in its extracellular and transmembrane domains. It has several alternatively spliced isoforms that affect its cytoplasmic domain (Pham-Dinh et al. 1995; Ballenthin and Gardinier 1996). A significant hydrophobic segment in the cytoplasmic domain has been suggested to be a membrane-binding site (Kroepfl et al. 1996); however, not all isoforms have this segment in their sequence. MOG is one of the most important and most intensively studied autoantigens of multiple sclerosis (Berger and Reindl 2000; Iglesias et al. 2001; Lalive 2008).

Myelin protein 2 (P2) is a member of the fatty acid-binding protein family (Storch and Thumser 2010), specifically expressed in the myelin sheath, where it is thought to play roles in both lipid transport and structural integrity of the myelin sheath. We have recently determined the crystal structure of human P2 (Majava et al. 2010a) and shown that it can both stack lipid bilayers (Suresh et al. 2010) and affect their dynamics (Knoll et al. 2010). Peptides from P2 are autoantigens in experimental autoimmune neuritis (EAN) (Hahn et al. 1991; Rostami and Gregorian 1991), and P2 is also one of the candidate autoantigens in the human autoimmune peripheral neuropathy Guillain–Barré syndrome (Hahn et al. 1991; Rostami and Gregorian 1991).

The 2′,3′-cyclic nucleotide 3′-phosphodiesterase (CNPase) is a highly abundant enzyme in myelin, with an unknown function. It has two folded domains (Myllykoski and Kursula 2010) plus a C-terminal tail that links the protein to the plasma membrane. Recently, CNPase has been suggested to be potentially involved in schizophrenia (Peirce et al. 2006; Voineskos et al. 2008) and multiple sclerosis (Muraro et al. 2002; Lovato et al. 2008). The structure of the catalytic phosphodiesterase domain is known (Sakamoto et al. 2005), and the C-terminal membrane-binding peptide has also been studied structurally (Esposito et al. 2008).

Here, we used synthetic peptides and membrane-mimetic conditions (detergent micelles and TFE) as a simplified model system to study the interactions of different segments of myelin-specific proteins with the lipid bilayer cytoplasmic surface. Such systems have been used before for similar purposes rather extensively (Prevost et al. 2000; Trifilieff 2005; Andrushchenko et al. 2006; Esposito et al. 2008; Wahlstrom et al. 2008; Ahn et al. 2009; Gobl et al. 2010; Le Lan et al. 2010). We used synchrotron radiation circular dichroism spectroscopy (SRCD) to characterize the conformation of the myelin protein-derived peptides in different environments and note significant spectral differences due to conformational changes.

Materials and methods

Synthetic peptides and chemicals

Several myelin proteins, known to interact with the membrane surface, were analyzed with respect to putative membrane-binding peptides, using e.g. literature data, secondary structure predictions and Amphipaseek (Sapay et al. 2006). The peptides corresponding to these regions were purchased from SBS Genetech (Beijing, China) and dissolved at a concentration of 10 mg/ml in 10 mM potassium phosphate, pH 7.0. The concentration used was based on the information provided by the vendor based on their accurate peptide synthesis. The N-termini of the peptides were acetylated and the C-termini amidated, unless indicated otherwise (Table 1). The DPC and DDAO (n-dodecyl-N,N-dimethylamine-N-oxide) were purchased

Table 1 Peptides used in the current study

Peptide	Sequence	Residues
P0 juxtamembrane	RYC(pal)WLRRQAALQRRL	151–165
CNPase C-terminus	SRKGGALQSC(pal)TII-COOH	408–420
MOBP internal repeat	PRSPPRSERQPR	96–107,106–117,116–127,126–137
MOBP C-terminus	SRGGSPVKASRFW-COOH	170–182
P2 N-terminus	SNKFLGTWKL	1–10
MOG 20.5 kDa C-terminus	LHRTFGQFLEELRNPF-COOH	161–177
MOG juxtamembrane	LQYRLRGKLRA	147–158

The palmitoylation sites (pal) and unmodified C-termini (COOH) are indicated, where applicable. All sequences correspond to those of the human proteins

from Anatrace, and SDS (sodium dodecyl sulfate) and TFE from Sigma.

Synchrotron radiation CD spectroscopy

SRCD data were collected on the beamline 3m-NIM-C at BESSY (Berlin) and processed essentially as previously described (Majava et al. 2010b). The samples were prepared by mixing the peptides at a final concentration of 1 mg/ml with different detergents at 0.5% or TFE at 30%, in a buffer containing 10 mM potassium phosphate, pH 7.0. Three spectra were collected in a 100-μm quartz cuvette between 260 and 175 nm and averaged, and a similarly measured spectrum of the corresponding buffer was subtracted. Some of the peptides were insoluble in the phosphate buffer alone and for them only spectra with detergents and TFE were measured. The SRCD spectra were deconvoluted within the wavelength range 178–260 nm using the tools at Dichroweb (Lobley et al. 2002), mainly the CDSSTR algorithm (Compton and Johnson 1986) and the SP175 reference data set (Lees et al. 2006).

Results and discussion

Selection of peptides for the study

The peptides represented either previously known or predicted membrane-associated segments of myelin proteins. Secondary structure predictions and propensity to form amphipathic helices were considered, in addition to earlier literature data, while selecting the peptides. It should be noted that the P2 peptide was already used for DPC-binding assays with fluorescence spectroscopy in our earlier study (Majava et al. 2010a). The peptides used in this study are listed in Table 1, and the helical wheel projections are given in Online Resource 1.

The P0 peptide was a thiopalmitoylated derivative of the juxtamembrane domain at the cytoplasmic side of its single transmembrane domain. Cys153 is known to be acylated in vivo, and the attached lipid moiety is generally palmitate in higher vertebrates (Bizzozero et al. 1994; Bharadwaj and Bizzozero 1995; Gao et al. 2000; Xie et al. 2007). Recently, a similar peptide (residues 152–171) was used to show that thiopalmitoylation of Cys153 increased the immunogenicity of this peptide in a rat model (EAN) (Beaino and Trifilieff 2010).

The CNPase peptide corresponds to the C-terminus of the protein, which is known to be isoprenylated at Cys417, the fourth residue from the C-terminus, and attached to the membrane (Braun et al. 1991; Cox et al. 1994; De Angelis and Braun 1994; De Angelis and Braun 1996; Bifulco et al. 2002). Also palmitoylation has been experimentally detected (Agrawal et al. 1990). The peptide used here, corresponding to the 13 C-terminal residues, was palmitoylated at Cys417 and proved to be insoluble in buffer. Our previous data indicate that when this region is included in a recombinant form of CNPase, the high reactivity of the Cys residue results in a covalent dimerization of the recombinant protein via a disulfide linkage (Myllykoski and Kursula 2010).

The two MOBP peptides represented a single internal repeat, from the repeat domain present in the longer alternatively spliced isoforms, and the C-terminus of the longest isoform. At its N-terminus, MOBP is likely to fold into a FYVE domain (Kursula 2008), which is also predicted to be a membrane-binding domain. The peptides used were selected from outside the predicted FYVE domain to find out whether the repeat domain or the C-terminus would behave as membrane-binding sites.

For P2, the peptide corresponds to the 10 N-terminal amino acids of the human protein; using Trp fluorescence, we have previously detected interactions with DPC micelles using this peptide and the full-length protein (Majava et al. 2010a). We have also mapped the location of this segment within the 3D structure of the human P2 protein, where it forms a short helix-like structure and part of the first β-strand (Majava et al. 2010a).

For MOG, two peptides were selected, corresponding to a putative membrane-binding site in the very beginning of the cytoplasmic domain and the C-terminus of the 20.5-kDa isoform. MOG is an integral membrane protein, which is suggested to have additional membrane-binding sites within its cytoplasmic domain (Kroepfl et al. 1996). Usually, the hydrophobic patch in the cytoplasmic domain has been assigned this role; neither of the peptides used here are parts of the hydrophobic domain.

Folding of potential membrane-associated peptides from myelin proteins

SRCD spectra from the peptides were collected in the presence of 0.5% DPC, SDS and DDAO micelles, as well as 30% TFE and phosphate buffer alone. While SDS is an anionic compound with a sulfate head group, DPC has a zwitterionic phosphocholine and DDAO an amine oxide head group. The attached hydrocarbon chain is a dodecyl group in all three detergents. TFE is a commonly used membrane-mimicking organic compound, which is known to induce helical conformation in a number of proteins and peptides.

Since the main goal was the comparison of the peptides under different conditions, all measurements were carried out at a constant peptide concentration of 1 mg/ml, and no further corrections to the spectra were applied. Specific

conformation-dependent features of the SRCD spectra were used to follow the respective peptide folding properties; these included (1) the presence of a strong negative peak at 200 nm for an unfolded peptide, (2) the characteristic minima (208 and 220 nm) and maximum (195 nm) for α-helical structure and (3) a minimum at 218 nm for a β-stranded structure. In general, the observation of a shift of the 200-nm minimum toward a higher wavelength is a sensitive indicator for even small amounts of folding and loss of random coil structure. Some of the spectra were also quantitatively analyzed using the Dichroweb server (Lobley et al. 2002), but many of the spectra could not be deconvoluted using the available algorithms, and thus a systematic quantitative analysis of all the spectra was considered to be relatively uninformative compared to the visual comparison of the measured spectra.

The P0 peptide was insoluble in the buffer and was only measured with detergents and TFE (Fig. 1a). A strong helical signal was observed in DPC and SDS (19%), but the peptide was essentially unfolded in DDAO. In TFE, the peptide was more helical (37%) than in DPC or SDS. The result indicates a clear helical propensity for the peptide, but a phosphate mimic (phosphocholine or sulfate) seems to be required for folding in the case of micelles. It is likely that the acyl group as well as the aromatic and Leu side chains are embedded inside the micelle, while the 5 Arg residues interact with sulfate/phosphate moieties on the micelle surface.

The palmitoylated CNPase C-terminus was insoluble both in phosphate buffer and in TFE. While it was solubilized with all three detergents, the CD spectrum suggests mainly a random coil structure (Fig. 1b). It should be noted that there is a strong positive maximum at 185 nm, which is usually not seen for unfolded peptides, and indicates a specific secondary structure, such as a short β-strand or a turn. This peak is stronger in SDS and DPC than DDAO. In fact, a deconvolution of the spectrum measured in DPC indicates fractions of approximately 20–25% for both β-strand and turn, and approximately 50% random coil. The results are different from those obtained in a previous study (Esposito et al. 2008), where a more prominent helical conformation was observed; a clear explanation for the difference is not obvious. While our peptide was palmitoylated at its Cys residue, the study by Esposito et al. used a peptide synthesized with 2-amino-octadecanoid acid at the corresponding position. We also employed a different pH in the SRCD measurement compared to the CD experiment by Esposito et al. and apparently, their NMR experiments were carried out unbuffered. While these points may explain the different behavior of our peptide in the presence of detergent micelles, the conclusion is that the C-terminus of CNPase may also bind to micelles in a non-helical conformation. This region has been shown to be important both to membrane and tubulin binding of CNPase (Bifulco et al. 2002).

For both of the MOBP peptides, CD spectra indicating a fully disordered structure was obtained in all tested conditions (Fig. 2). This implies that these peptides do not have specific interactions with the micelles or induced folding in membrane-like environment. It is likely that the main membrane-binding site in MOBP is indeed the FYVE domain, the only part of the MOBP sequence, which is present in all MOBP splice isoforms. The repeat region of MOBP could act as a molecular ruler or an interaction site for other proteins.

Recently, we suggested that the N-terminus of P2 could be a membrane-binding site (Majava et al. 2010a). The SRCD spectra show that while the peptide is fully unfolded

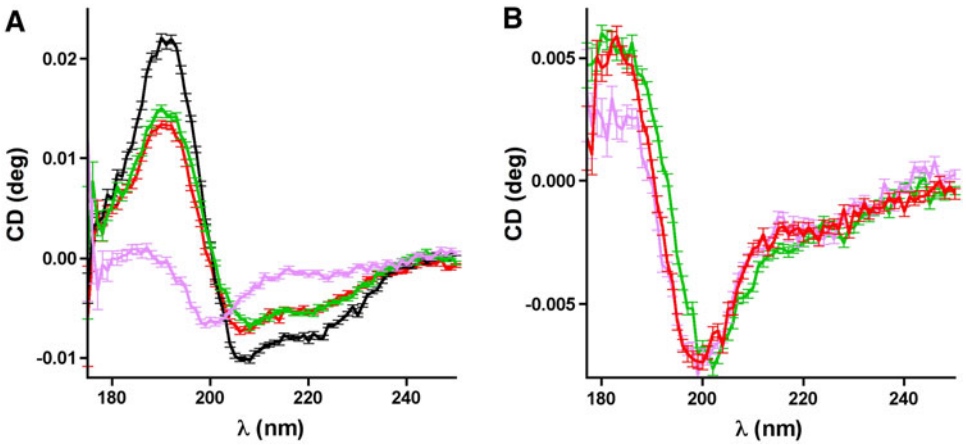

Fig. 1 SRCD spectra of the thiopalmitoylated peptides from P0 (**a**) and CNPase (**b**). In all figures, the following color scheme is used: *blue* phosphate buffer, *red* DPC, *green* SDS, *magenta* DDAO, *black* TFE. The P0 peptide was not soluble in phosphate buffer, and the CNPase peptide only in detergent solutions. All CD spectra in the current study were measured at a constant concentration, thus allowing for a direct comparison between all peptides and conditions (color figure online)

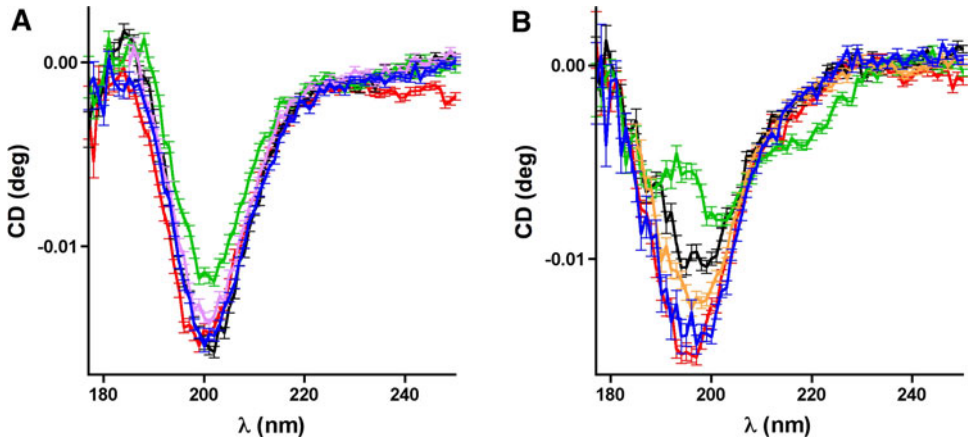

Fig. 2 The peptides from MOBP. Both the internal repeat peptide (**a**) and the C-terminal peptide (**b**) are affected very little, if at all, by membrane mimicking conditions

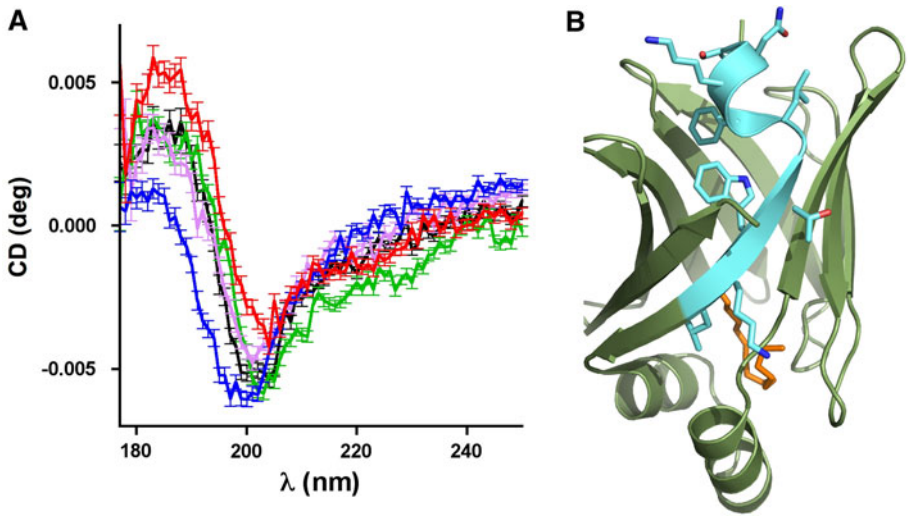

Fig. 3 The N-terminal peptide from P2 and its mapping onto the 3D structure of human P2. **a** SRCD indicates small conformational changes in the P2 peptide, which are most pronounced in DPC. **b** The crystal structure of human P2 (PDB entry code 2WUT) (Majava et al. 2010a), in which residues 1–10 are highlighted in *cyan*, with the side chains shown. It is possible that a small conformational change in this region assists in membrane surface binding. The bound palmitate molecule inside the barrel is shown in *orange* (color figure online)

in aqueous buffer, it obtains a small degree of folded structure in all membrane-mimetic conditions, as highlighted by the shift of the major negative peak from 200 nm to higher wavelengths and the appearance of a positive peak at around 190 nm (Fig. 3a). The effect is strongest with DPC and SDS, in which also a small negative trough is observed at 220 nm; all these attributes hint at a small amount of α-helix. While in the crystal structure, this sequence forms a 1-turn helical structure followed by the beginning of the first β-strand (Fig. 3b), it is possible that the N-terminus would change its conformation upon membrane surface binding.

MOG is an integral membrane protein, with an additional second hydrophobic domain within its C-terminal cytoplasmic domain that has been suggested to be a membrane anchor. The peptides we used here are not from this hydrophobic domain, but rather represent the immediate juxtamembrane domain after the transmembrane helix and the C-terminus. Both peptides have the potential to fold into amphipathic helices based on the sequence (Online Resource 1). The C-terminal peptide (from the alternatively spliced 20.5-kDa isoform that lacks the second hydrophobic domain) was insoluble in buffer, and to a limited extent in TFE. In all three detergents, however, the peptide was soluble and gave a strong CD spectrum for α-helical structure (Fig. 4a), estimated to be 44% helical at most, in DPC. The juxtamembrane peptide remained unfolded in buffer and DDAO, but folded into a helical structure when incubated with DPC, SDS and TFE (Fig. 4b). When binding to micelles (and lipid bilayers), it is likely that the three arginine residues within the peptide interact with phosphate (or sulfate) head groups, assisting in binding and folding.

Implications for myelin protein interactions with the membrane surface

Myelin contains several specific proteins that all are in intimate contact with the membrane surfaces, yet belong to completely different structural classes. Our purpose was to obtain more information on the possible conformations of myelin protein segments that are putative membrane surface interaction sites.

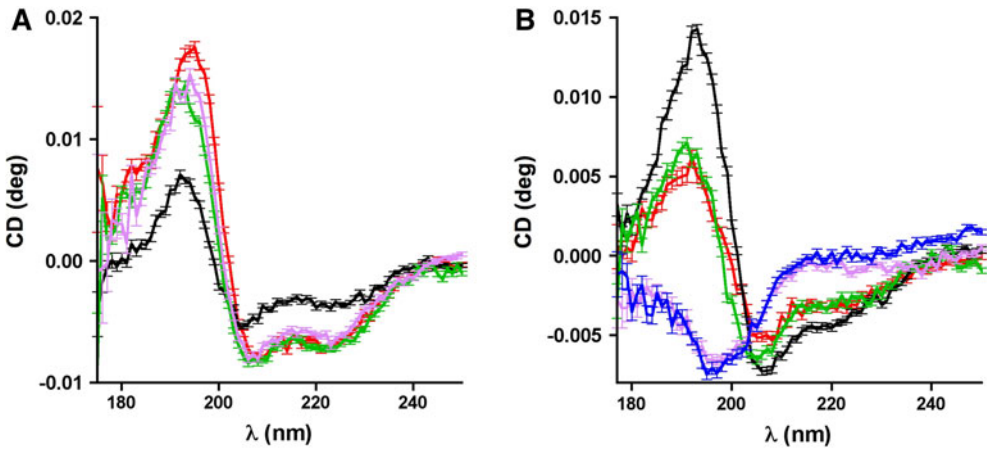

Fig. 4 SRCD spectra of the MOG peptides. The C-terminal (**a**) and the juxtamembrane (**b**) peptides both fold into helical structures in membrane-mimetic conditions. For the C-terminal peptide, the effect is strongest with detergent micelles, while the juxtamembrane peptide folds more efficiently in TFE

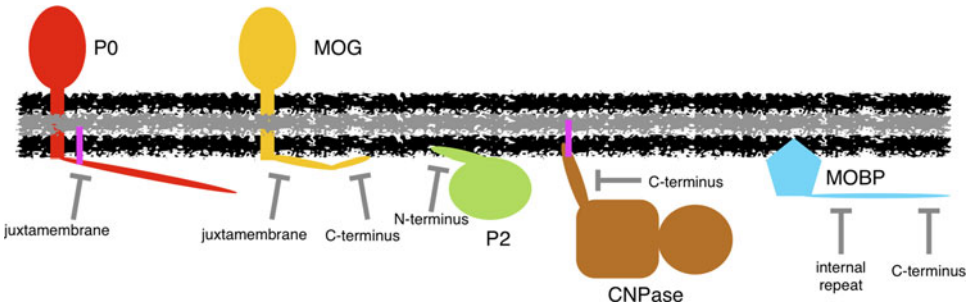

Fig. 5 A schematic view of the discussed proteins, and their known or predicted binding modes to the lipid bilayer. The approximate locations of the peptides used in this study are indicated, and the positions of the palmitate moieties in the peptides are shown in *magenta*. The MOG isoform shown represents the 20.5-kDa isoform, which is missing the additional hydrophobic domain in the cytoplasmic side. In the current study, we have obtained novel evidence for membrane-binding segments in the juxtamembrane and C-terminal sites of MOG and the N-terminus of P2. We also have shown the interaction of the CNPase C-terminus with micelles without folding into a helical structure, and provided data apparently ruling out membrane interactions by the MOBP repeat domain and its C-terminus

The studied proteins are shown schematically in Fig. 5. Interestingly, both of the juxtamembrane peptides, from P0 and MOG, folded into a helical conformation. On the other hand, of the 3 C-terminal peptides, that of MOBP seemed to have no interaction with micelles, that of MOG folded into a helix, and that of CNPase, though becoming solubilized, did not show large fractions of helical secondary structure. The N-terminal peptide from P2 showed some degree of conformational change in different conditions, indicating that it may be able to interact with membranes in a way not evident from the crystal structure. All in all, the results indicate different modes of binding to micelles and conformational changes for the peptides from different myelin proteins.

While we do recognize that detergent micelles or organics cannot fully represent the properties of the myelin lipid membrane, they have been widely used to mimic the membranous environment—also in the case of a myelin protein, MBP (Fares et al. 2006; Libich and Harauz 2008; Bamm et al. 2010). Specifically, the head group of DPC is chemically equivalent to the head group of phosphatidylcholine in bilayers, and the interactions between peptides and membranes can be mimicked by using a micellar environment. We are planning to extend the study toward using membrane vesicles and oriented bilayers in the future. Further studies on myelin peptides and their membrane interactions are clearly warranted, and experiments such as oriented CD spectroscopy and solid-state NMR in lipid bilayers will further illuminate the details of the binding modes of myelin proteins to membrane surfaces.

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