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The Role of Phosphoinositides in the Interaction of Myelin Basic Protein with the Oligodendroglial Cell Membrane

The only protein known to be essential for myelin formation and compaction in the central nervous system is myelin basic protein (MBP). Oligodendrocytes in mutant mice that lack MBP-expression are unable to deposit a functional myelin sheath and the few lamellae formed around axons are not compacted. The association of MBP as a positively-charged protein with negatively charged membranes is therefore crucial for myelination, but the mechanisms by which MBP associates with the myelin membrane remains elusive. In this study, I demonstrate that the signaling lipid phosphatidylinositol (4,5)-bisphosphate (PIP2) is important for the stable association of MBP with cellular membranes. This association is lost upon specific reduction of PIP2 levels following the overexpression of a phosphoinositide-5-phosphatase (Synaptojanin 1) that selectively hydrolyzes PIP2. The association is also lost through elevated intracellular Ca^{2+} levels. Moreover, since MBP interacts with the membranes electrostatically, the experimental decrease of membrane charges at the intracellular membrane surface (through PIP2 dephosphorylation) was shown to cause the dissociation of MBP from the plasma membrane. Experiments presented here further implicate that one putative PIP2 binding domain of MBP lies within the exon-1 encoded region. The relevance of this protein-lipid interaction was demonstrated for the corpus callosum of mice, analyzed by electron microscopy after reducing membrane surface charges in acute brain slices. Here, PIP2 hydrolysis led to the loss of myelin compaction. A related phosphoinositide that might play a role in myelin formation is the signaling lipid phosphatidylinositol(3,4,5)-trisphosphate (PIP3). We found PIP3 and some downstream polarizing factors to be accumulated at the tips of growing cellular processes in both immortalized and primary oligodendrocytes. Taken together, the results presented here demonstrate that PIP2 and PIP3 play an important role in MBP association to the plasma membrane and oligodendroglial polarity. This association might induce the formation of lipid clusters, which could serve as a signalling platform for polarization of oligodendrocytes through PIP3 signalling. These findings provide a novel link between phosphoinositol metabolism and MBP function in oligodendrocytes in development and disease.