GANGLIOSIDES OF THE CNS MYELIN MEMBRANE


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BACKGROUND

Myelin gangliosides have a number of unusual properties that set them apart from gangliosides of most other nervous system membranes. One is their low concentration, which in the case of rat amounts to about one-tenth that in synaptic plasma membranes. This may account for the fact that when first detected in isolated myelin\(^1,2\) they were believed to represent neuronal contamination. Subsequent studies of Suzuki and coworkers\(^3,4,5\) provided strong if not conclusive evidence that they are intrinsic to myelin itself. A key finding in those studies was the distinctive pattern of molecular distribution, the main feature of which was a high proportion of G\(_{\text{M1}}\). The same phenomenon was later observed in myelin from man\(^6\) and mouse\(^7\). We have undertaken a survey of several other vertebrates to assess possible variations in pattern and concentration.

Another distinctive feature is the presence of sialosylgalactosyl ceramide (G\(_{\text{M4}} = G_7\)) in at least some species. In mature human myelin it accounts for 15-20% of total myelin ganglioside. This unusual ganglioside, shown to be closely related structurally\(^6\) and probably
metabolically to myelin galactosyl ceramide, was barely detectable in gray matter and completely undetectable in peripheral nerve and extraneural tissues. The recent demonstration of $\text{GM}_4$ in isolated human oligodendroglia indicated its probable biosynthetic origin; that study indicated a limited pool size in these cells with over 85% of white matter $\text{GM}_4$ being localized in myelin. Study of mouse brain myelin revealed considerably lower levels of $\text{GM}_4$ while data for other species showed further wide variations in regard to this component (see below).

Finally, unusual developmental changes constitute yet another distinctive feature of myelin gangliosides. Thus, myelin from young rats, while still possessing $\text{GM}_1$ as the major component, had relatively more di- and trisialogangliosides than the adult pattern. $\text{GM}_4$ also shows an increase in development but on a different time-scale than $\text{GM}_1$; in the mouse it was undetectable until 35 days of age, after which it slowly increased over several months. Human myelin also showed increasing $\text{GM}_4$ with age. An additional aspect of development was revealed in the fact that total ganglioside concentration in mouse myelin doubled between the youngest (23 days) and oldest (490 days) animals. This is very likely a species-related phenomenon.

ORIGIN OF MYELIN GANGLIOSIDES

While the studies cited above support the concept of gangliosides as true myelin constituents, the evidence in toto does not rigorously exclude the possibility that they might belong to contaminating structures. Residual quantities of tightly adhering membranes could, depending on their composition, account for a greater or lesser portion of the observed ganglioside. The axolemma membrane is of particular concern in this regard because of indications that it adheres tightly to myelin during the isolation process and that it has a relatively high ganglioside concentration.

To study this question we exploited the finding of DeVries that EGTA is an effective agent for stripping axolemma from myelin. This was analogous to the report