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EDITORIAL OPEN ACCESS

Putative effects of neurofilaments released during multiple sclerosis

Catherine Fressinaud

Lesions in multiple sclerosis (MS) are characterized by inflammation, oligodendrocytes (OL) death and demyelination as well as axon lesions. The remyelination failure associates with persistent axonal alterations [1, 2], and this results in permanent disability for patients. These axon lesions can occur early in the course of the disease [3], but their origin is equivocal. They could result directly from inflammation, or they could be secondary to prolonged demyelination [4]. It is striking that experimentally remyelination alleviates them [5, 6].

Axon alterations are characterized by dystrophy [7], axon section [1], decreased expression of axon cytoskeleton proteins: i.e. neurofilaments (NF) [1, 8], tubulin, as well as tau, and GAP43 [8]. They are mainly observed in the demyelinated lesions. Whether this axon cytoskeleton impairment alters or not remyelination is unknown. Clearly, it has been demonstrated that modifications of expression of other axon proteins such as PSA-NCAM, and paranodin [9, 10], inhibit remyelination in vitro. In MS lesions the presence of OL in contact with axons, and lacking proper differentiation in order to undertake their remyelination [11], suggests that signal from damaged axons is inappropriate to trigger remyelination. Whether decreased NF expression is involved in this process is unknown, however as these proteins are intracellular they could not directly act on OL under normal conditions.

Catherine Fressinaud[1,2]
Affiliations: [1]LUNAM, Neurology Department, University Hospital, 4 rue Larrey, 49933 Angers Cedex 9, France; [2]LUNAM, Neurobiology and Transgenesis Laboratory - UPRES EA 3143, University Hospital, 4 rue Larrey, 49933 Angers Cedex 9, France.
Corresponding Author: Dr. Catherine Fressinaud, MD, PhD; Neurology Department, University Hospital, 4 rue Larrey, 49933 Angers Cedex 9, France; E-mail: catherine.fressinaud@univ-angers.fr

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In addition to these pathological characteristics, NF have been identified by several groups in the cerebrospinal fluid (CSF) of patients during relapses [12, 13]. The concentration of NF is correlated with the severity of the disease (relapse rate and disability) [4, 14–16]. However, the role and the fate of NF in the extracellular space are unknown. Macrophages containing debris immunostained for NF light chain (NFL) have been observed in plaques [17]. Reports on this subject indicate that experimentally NF are susceptible to proteolysis [18, 19]. Interestingly, NF proteolysis is altered in experimental autoimmune encephalitis (EAE), an animal model of MS [20].

Some results in vitro suggest that NF purified from rat brain, and synthetic peptides containing the tubulin-binding site (TBS) of NFL [21], the light chain of NF, as well as other cytoskeleton proteins such as tubulin, increase the proliferation of OL progenitors, and/or the maturation of OL [22, 23]. This is observed under basal conditions, and also when OL cultures are treated with demyelinating chemicals such as lysophosphatidyl choline (LPC) [23, 24]. So, NF and their associated proteins partially protect OL from a demyelinating event in vitro. This occurs after the uptake by endocytosis of NF, and of NF-TBS peptides, by cells of the OL lineage, although no specific receptor has been identified [25].

According to these results, we hypothesize that after a first demyelinating event in vivo the release in the extracellular space of native (unaltered) isoforms of axon cytoskeleton proteins such as NF could increase remyelination by OL. This would finally result in the restoration of the axon integrity. On the contrary, after several relapses the release of abnormal NF isoforms [15] would be unable to stimulate remyelination by OL. Persistent demyelination and axon loss would follow. This hypothesis would have to be tested in vivo in demyelinating models of MS [6].

The detection of NF in blood samples [26, 27] could facilitate the study of this phenomenon. It will allow establishing more precisely correlations between relapses, NF alterations and their release, and axon degeneration detected by MRI scan [28].

Keywords: Neurofilaments, Putative effects, Sclerosis

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Catherine Fressinaud – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

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Conflict of Interest

Authors declare no conflict of interest.

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