Demyelination of the Peripheral Nervous System Causes Neurologic Signs in Myelin Basic Protein-Induced Experimental Allergic Encephalomyelitis

Implications for the Etiology of Multiple Sclerosis

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Experimental allergic encephalomyelitis (EAE) is an autoimmune disease induced by inoculation with whole central nervous system (CNS) tissue, myelin basic protein (MBP), or myelin proteolipid protein. It is widely studied as a model of multiple sclerosis (MS), a human CNS demyelinating disease of unknown etiology. In MS, CNS demyelination is a major cause of neurologic signs. However, because of the reported absence of demyelination in some animals with neurologic signs of EAE, it has been suggested that the signs of EAE, especially acute EAE, are due not to demyelination but to other factors such as edema. But these reported studies failed to use adequate histologic techniques to assess demyelination or to thoroughly examine the whole nervous system, particularly the lumbar, sacral, and coccygeal spinal cord and the peripheral nervous system (PNS), which is known to be involved in EAE. We recently showed in rabbits and rats with whole spinal cord-induced acute EAE that there is ample demyelination in the PNS and CNS to account for the neurologic signs. I am reporting that, in MBP-induced acute EAE in the Lewis rat, the ventral and dorsal spinal roots are principal sites of demyelination, whereas the spinal cord and brain are only slightly demyelinated, although considerably inflamed.

MBP was prepared from guinea pig spinal cord (after removal of the spinal roots) by the method of Deibler et al., and its purity was ascertained by sodium dodecyl sulfate polyacrylamide gel electrophoresis. MBP in 0.9% saline solution was emulsified in an equal volume of incomplete Freund's adjuvant containing 4 mg/ml of Myco-

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bacterium butyricum. Male rats, 8-10 weeks old, received 0.1 ml of emulsion in a footpad of each hindfoot. The total dose of MBP was 50 μg per rat. Light and electron microscopic histologic studies were performed on rats with hindlimb weakness, as previously described. These studies demonstrated inflammation and mild demyelination in the spinal cord and brainstem (Fig. 1). However, the principal sites of demyelination were the lumbar, sacral, and coccygeal ventral and dorsal spinal roots (Fig. 2). The vast majority of random 0.5-2 μm sections through individual spinal roots showed demyelination. Electrophysiologic studies indicated that this PNS demyelination is an important cause of the neurologic signs in these animals (Pender, in preparation). There was minimal involvement of the dorsal root ganglia and peripheral nerves.

Thus, in the Lewis rat, immunization with MBP results in a demyelinating polyarthritis with little CNS demyelination. PNS demyelination is an important cause of the neurologic signs of acute MBP-EAE in these animals and is due to the close similarity, if not identity, of CNS MBP and PNS P, protein. The predominance of spinal root demyelination over CNS demyelination may be due to a lesser blood-tissue barrier in the roots. In contrast, it has recently been reported that T-cell lines and clones specific for MBP induce considerable CNS demyelination in irradiated nude mice. Differences in the distribution of demyelination in rats and mice could be due to interspecies differences in the blood-nerve barrier, Is antigen expression, or MBP concentration in the spinal roots or to differences in MBP epitopes in intact
CNS and PNS myelin. Sensitization to MBP may account for the PNS involvement in patients developing neurologic complications after inoculation with antirabies vaccine containing sheep brain. Although MS may sometimes involve the PNS, the neurologic signs of MS are generally regarded as being due to CNS demyelination. If MBP is the target antigen in MS, the relevant epitope must be recognized in CNS but not in PNS myelin.

FIGURE 2. Longitudinal section through an S4 ventral root of a rat with MBP-induced acute EAE 3 days after the onset of tail weakness. Demyelinated axons are present (arrows). Mononuclear cells containing myelin debris (arrowheads) lie adjacent to some of the demyelinated axons. HistoResin (LKB Bromma) section stained with cresyl violet. Bar = 25 μm.

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FIGURE 2. Longitudinal section through 25 ventral root of rat with MBP-induced acute axonal injury (LVH, brown) section stained with crystal violet. Bar = 75 "jum."

If MBP is the major antigen in MS, the T cell response must be considered in CNS neuropathic injury. Although MS may sometimes involve the CNS, the disease spectrum that encompasses CNS pathology. In patients developing autoimmune encephalopathy with simultaneous acute and chronic signs of MS are generally regarded as having due to CNS demyelination. Neuroinflammatory mechanisms must be understood for the CNS involvement.