

Peroxynitrites in MS

Research has suggested that cell damage in MS is related to the production of the molecule peroxynitrite. This was first proposed in 1992 by Louis Ignarro(1), Nobel Prize winner in 1998 for his work on nitric oxide in cardiovascular disease. Indirect evidence of nitric oxide involvement in MS was published by Boullerne et al (2) in 1995. In 1998 Giovannoni (3) demonstrated the presence of nitric oxide metabolites in the cerebrospinal fluid of MS patients which further supported Ignarro's hypothesis. Further evidence came from another study published in 1998 by Cross et al (4) where nitrotyrosine was found in MS lesions at post mortem. They further showed that nitric oxide metabolites in CSF increased during clinical relapses of MS. Scott et al (5) found that oligodendrocytes in rats exposed to peroxynitrites were damaged with increased DNA strand breakage and reduced mitochondrial activity. Touil et al (6) also showed in animal studies that peroxynitrites led to myelin disorganisation and axonal damage presenting similarities to MS lesions.

Calabrese et al (7) demonstrated the presence of inducible nitric oxide synthase (iNOS) in the CSF of MS patients which was absent in controls. Nitrotyrosine was present in greatly increased amounts in the CSF of MS patients indicating peroxynitrite activity. This strongly suggested that nitrosative stress was implicated in the pathogenesis of MS.

Danilov et al (8) showed that nitric oxide products were present in all three types of MS (RRMS, PPMS and SPMS) as measured in CSF of 61 patients. There were greater levels of these oxidation products during exacerbations of the disease than in the stable progressive phases of the disease. They suggested that nitric oxide products could be used as a surrogate marker of disease activity.

Rejdak et al (9) examined the nitric oxide metabolites in patients with all three types of MS and controls. Interestingly they found that the nitric oxide metabolite levels were higher in those with less disability but that there was a correlation with the volume of Gd – enhanced lesions on MRI. Having raised baseline CSF nitric oxide metabolite levels was associated with clinical and MRI

progression at 3 years follow up. In a further study by this author (10) they concluded that nitrosative stress is likely to be relevant to the development of sustained disability in MS patients.

Lui et al (11) from Harvard Medical School showed inducible nitric oxide and nitrotyrosine was present in post mortem MS lesions strongly suggesting a role for nitric oxide in MS. Scott et al (12) demonstrated peroxynitrite production in brain derived cells in 2007 and in the same year Jack et al (13) showed that brain cells were susceptible to damage by peroxynitrites but not nitric oxide itself using nitrotyrosine as a marker of peroxynitrite production. In 2008 Gonsette (14) showed that peroxynitrites are associated with acute MS lesions as well as contributing to ongoing neurological damage in the chronic phase of the disease.

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