A possible peripheral TNF-a modulation of glutamate impairment in MS neurodegeneration

M Gironi[1,3], CP Zoia[2], M. Vaghi3, M. Rovaris[1], M. Saresella[1] , E. Mariani[3], R. Nemni[1], M. Clerici[1], P. Compagnoni[2], M Frigo[4], G Cavaletti[2,4] and C Ferrarese[2,4]

[1]Fondazione Don Carlo Gnocchi, IRCCS, Milano, Italy
[2]Department of Neuroscience and Biomedical Technology, University of Milano-Bicocca,
3 CAM, Polidiagnostic Center, Monza
[4]Department of Neuroscience, San Gerardo Hospital, Monza, Italy

Objective: Neurodegeneration in Multiple Sclerosis (MS) is a multifactorial process involving glutamate-excitotoxicity and inflammation. Glutamate (glu) levels are finely regulated by glu transporters (EAATs). T-cell derived TNF-a impairs glu clearance capacity of astrocytes providing a pathogenic link to glu excitotoxicity that may contribute to early axonal dysfunction remote from active autoimmune inflammatory demyelination (1) Moreover, anti-TNF-a therapy in EAE shows mixed results, whereas in MS trials it increases CNS immune activation and disease activity. It is clear that TNF-a not only exerts proinflammatory and cytotoxic effects but is also essential for the subsequent suppression of inflammation, repair and regeneration in the CNS (2). We investigated a putative TNF-a modulation, driven by immune cells, on EAATs function in peripheral system.

Methods: in 17 primary-progressive, 16 secondary-progressive, 25 relapsing- remitting and 12 benign MS patients and 60 Healthy controls, Sodium/energy-dependent-glutamate-uptake was studied in platelets, measuring [H^3]-Glu by beta-counter.
Preliminary TNF-a plasma levels were analyzed by commercial ELISA kit (eBioscience).

Results: Reduced glu-uptake values were found in MS compared to controls ($p<0.005$). Representative saturation curves showed Vm was significantly decreased (HC= 218, MS=56), whereas Km(HC=53, MS=48.5) was unaffected. Interestingly benign showed higher glu-uptake ($p<0.01$) compared to other MS groups.
Reduced plasma TNF-a levels were preliminary observed in MS compared to HC and benign MS ($p<0.05$).

Conclusions: Our data suggest that the glu-uptake impairment may be modulated by TNF-a also in peripheral cells as in astrocytes, even if further investigations will be need. Moreover, a different trend seems to be evident in benign patients versus other MS groups. However, the relationship between glu-uptake and immune system disequilibrium could be bidirectional, and mirror the CNS modulation pathway. Interacting with its receptors on Tcells, glu can also influence several lymphocyte functions. In turn, autoreactive Tcells infiltrating the brain, modulate TNFa release and impair EAATs functions at different levels in the disease ongoing.
Ref:(1) Korn, Magnus, and Jung, 2005; (2) Lim and Constantinescu, 2010