

Disruption of thiol homeostasis and nitrosative stress in the cerebrospinal fluid of patients with active multiple sclerosis: evidence for a protective role of acetylcarnitine.

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Recent studies suggest that NO and its reactive derivative peroxynitrite are implicated in the pathogenesis of multiple sclerosis (MS). Patients dying with MS demonstrate increased astrocytic inducible nitric oxide synthase activity, as well as increased levels of iNOS mRNA. Peroxynitrite is a strong oxidant capable of damaging target tissues, particularly the brain, which is known to be endowed with poor antioxidant buffering capacity. Inducible nitric oxide synthase is upregulated in the central nervous system (CNS) of animals with experimental allergic encephalomyelitis (EAE) and in patients with MS. We have recently demonstrated in patients with active MS a significant increase of NOS activity associated with increased nitration of proteins in the cerebrospinal fluid (CSF). Acetylcarnitine is proposed as a therapeutic agent for several neurodegenerative disorders. Accordingly, in the present study, MS patients were treated for 6 months with acetylcarnitine and compared with untreated MS subjects or with patients noninflammatory neurological conditions, taken as controls. Western blot analysis showed in MS patients increased nitrosative stress associated with a significant decrease of reduced glutathione (GSH). Increased levels of oxidized glutathione (GSSG) and nitrosothiols were also observed. Interestingly, treatment of MS patients with acetylcarnitine resulted in decreased CSF levels of NO reactive metabolites and protein nitration, as well as increased content of GSH and GSH/GSSG ratio. Our data sustain the hypothesis that nitrosative stress is a major consequence of NO produced in MS-affected CNS and implicate a possible important role for acetylcarnitine in protecting brain against nitrosative stress, which may underlie the pathogenesis of MS.

