Role of the microsomal prostaglandin E synthase-1 in cuprizone-induced demyelination and motor dysfunction.

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Multiple sclerosis (MS) is one of the most common demyelinating diseases. Microsomal prostaglandin E synthase-1 (mPGES-1) is a key enzyme that acts downstream of cyclooxygenase and plays a major role in inflammation and immune responses by converting prostaglandin (PG) H_2 to PGE_2. PGE_2 is highly produced in the cerebrospinal fluid of patients with MS. However, the role of mPGES-1 in MS has not been fully elucidated yet. In this study, we demonstrate the role of mPGES-1 in demyelination and motor dysfunction induced by cuprizone, one of the well established models of MS. Demyelination in the brain was induced in mice lacking mPGES-1 (mPGES-$1^{-/-}$ mice) and wild-type (WT) mice by feeding ad libitum with a powdered diet containing 0.2% cuprizone for 6 weeks under specific pathogen free condition. The expression of mPGES-1 in the brain was determined by real-time PCR. The cuprizone-induced demyelination was assessed by a myelin staining with coronal brain sections, and motor dysfunction was evaluated by the rotarod test. Cuprizone up-regulated the expression of mPGES-1 mRNA in the brain of WT mice. Interestingly, mPGES-$1^{-/-}$ mice exhibited lower degree of demyelination compared to WT mice. In addition, mPGES-1 gene deletion or COX-2 selective inhibitor celecoxib reduced cuprizone-induced motor dysfunction. These data indicate that COX-2/mPGES-1/PGE_2 system contributes to the pathophysiology of MS and open possible novel therapeutic approaches for MS.