Abdeslam Mouihate, J Neurol Neurophysiol 2018, Volume 9
DOI: 10.4172/2155-9562-C1-062

Ganaxolone reduces microglial activation associated with focal demyelination

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Introduction: Neuroinflammation is a major hallmark of demyelinating diseases. It involves the activation of astrocytes and microglia. Allopregnanolone, a positive modulator of GABAA receptor, is a therapeutic candidate for enhancing remyelination. However, its effect on demyelination-induced gliosis is still not unclear. In this study, we investigated the effect of ganaxolone (GNX), a synthetic analogue of allopregnanolone, on gliosis associated with demyelination.

Methods: Ovariectomized adult Sprague Dawley rats received a stereotaxic injection of 1% lysolecithin solution into the corpus callosum. This procedure induces a focal demyelination with known time course of de- and remyelination processes. Rats received daily injections of either dimethyl sulfoxide (DMSO) or GNX (i.p., dissolved in DMSO 2.5 mg/kg). The perilesion area of the corpus callosum was collected at three (peak of demyelination) or seven days (start of remyelination) after lysolecithin injection. Iba1, M1 (iNOS) and M2 (arginase-1) microglial markers were assessed using western blot. Triple immunofluorescent detection of GFAP, Iba-1 and myelin basic protein (MBP) was used to explore the extent of astrocyte and microglial activation, as well as myelin debris clearance by microglia at and around the demyelination lesion.

Results: Focal demyelination elicited a strong astrocytic and microglial activation at the site of demyelination. There was no significant difference in the expression of the microglial marker Iba1 or M1/M2 markers between vehicle-treated and GNX-treated rats three days post-lesion. On the other hand, GNX significantly reduced the density of microglia (Iba1+ cells) at the site of the lesion seven days post-demyelination. There was a slight decrease in the density of myelin debris at the center of the lesion in GNX-treated rats. GNX did not significantly affect the fraction of microglia containing myelin debris ($Iba1^+/MBP^+$), but significantly reduced that of microglia not containing MBP ($Iba1^+/MBP^-$). However, GNX did not affect the astrocytosis at the site of the demyelination lesion.

Conclusion: The allopregnanolone analogue GNX dampens demyelination-induced inflammation. This anti-inflammatory effect targeted microglia but not astrocytes. Furthermore, activation of GABAA receptors appears to heighten the clearance of MBP debris thus promoting a conducive environment for myelin recovery.

Grant support: Kuwait University Research Sector grant # YM02/16

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