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Metformin Therapy Attenuates Pro-inflammatory Microglia by Inhibiting NF- κ B in Cuprizone Demyelinating Mouse Model of Multiple Sclerosis

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Microglia polarization by methylprednisolone acetate accelerates cuprizone induced demyelination

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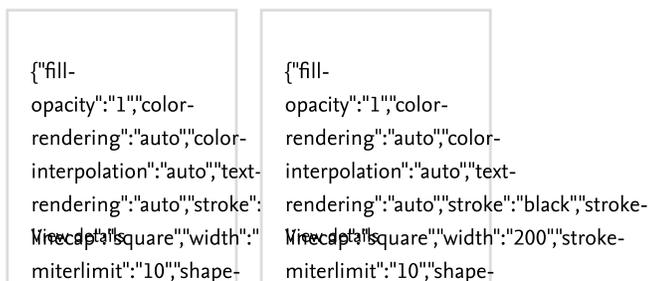
Abstract

Multiple sclerosis (MS) is a chronic disorder characterized by reactive gliosis, inflammation, and demyelination. Microglia plays a crucial role in the pathogenesis of MS and has the dynamic plasticity to polarize between pro-inflammatory (M1) and anti-inflammatory (M2) phenotypes. Metformin, a glucose-lowering drug, attenuates inflammatory responses by activating adenosine monophosphate protein kinase (AMPK) which suppresses nuclear factor kappa B (NF- κ B). In this study, we indirectly investigated whether metformin therapy would regulate microglia activity in the cuprizone (CPZ)-induced demyelination mouse model of MS via measuring the markers associated with pro- and anti-inflammatory microglia. Evaluation of myelin by luxol fast blue staining revealed that metformin treatment (CPZ + Met) diminished demyelination, in comparison to CPZ mice. In addition, metformin therapy significantly alleviated reactive microgliosis and astrogliosis in the corpus callosum, as measured by Iba-1 and GFAP staining. Moreover, metformin treatment significantly downregulated the expression of pro-inflammatory associated genes (iNOS, H2-Aa, and TNF- α) in the corpus callosum, whereas expression of anti-inflammatory markers (Arg1, Mrc1, and IL10) was not promoted, compared to CPZ mice. Furthermore, protein levels of iNOS (pro-inflammatory marker) were significantly decreased in the metformin group, while those of Trem2 (anti-inflammatory marker) were increased. In addition, metformin significantly increased AMPK activation in CPZ mice. Finally, metformin administration significantly reduced the activation level of NF- κ B in CPZ mice. In summary, our data revealed that metformin attenuated pro-inflammatory microglia markers through suppressing NF- κ B activity. The positive effects of metformin on microglia and remyelination suggest that it could be used as a promising candidate to lessen the incidence of inflammatory neurodegenerative diseases such as MS. © 2021, The Author(s), under exclusive licence to Springer Science+Business Media, LLC, part of Springer Nature.

Author keywords

Cuprizone ; Metformin ; Microglia activity; Multiple sclerosis ; Neuroinflammation; NF- κ B

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