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The Effects of Myelin Basic Protein Charge Isomers on the Methyl Cycle Metabolites in Glial Cells

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Abstract : Background: Multiple sclerosis (MS) is an inflammatory, neurodegenerative disease, which is accompanied by demyelination and autoimmune response to myelin proteins. Among post-translational modifications, which mediate the modulation of inflammatory pathways during MS, methylation is the main one. The methylation of DNA, also amino acids lysine and arginine, occurs in the cell. It was found that decreased trans-methylation is associated with neuroinflammatory diseases. Therefore, abnormal regulation of the methyl cycle could induce demyelination through the action on PAD (peptidyl-arginine-deiminase) gene promoter. PAD takes part in protein citrullination and targets myelin basic protein (MBP), which is affected during demyelination. To determine whether MBP charge isomers are changing the methyl cycle, we have estimated the concentrations of methyl cycle metabolites in MBP-activated primary astrocytes and oligodendrocytes. For this purpose, the action of the citrullinated MBP- C8 and the most cationic MBP-C1 isomers on the primary cells were investigated. Methods: Primary oligodendrocyte and astrocyte cell cultures were prepared from whole brains of 2-day-old Wistar rats. The methyl cycle metabolites, including homocysteine, S-adenosylmethionine (SAM), and S-adenosylhomocysteine (SAH), were estimated by HPLC analysis using fluorescence detection and prior derivatization. Results: We found that the action of MBP-C8 and MBP-C1 induces a decrease in the concentration of both methyl cycle metabolites, S-adenosylmethionine (SAM) and S-adenosylhomocysteine (SAH), in astrocytes compared to the control cells. As for oligodendrocytes, the concentration of SAM was increased by the addition of MBP-C1, while MBP-C8 has no significant effect. As for SAH, its concentration was increased compared to the control cells by the action of both MBP-C1 and MBP-C8. A significant increase in homocysteine concentration was observed by the action of the MBP-C8 isomer in both oligodendrocytes and astrocytes. Conclusion: These data suggest that MBP charge isomers change the concentration of methyl cycle metabolites. MBP-C8 citrullinated isomer causes elevation of homocysteine in astrocytes and oligodendrocytes, which may be the reason for decreased astrocyte proliferation and increased oligodendrocyte cell death which takes place in neurodegenerative processes. Elevated homocysteine levels and subsequent abnormal regulation of methyl cycles in oligodendrocytes possibly change the methylation of DNA that activates PAD gene promoter and induces the synthesis of PAD, which in turn provokes the process of citrullination, which is the accompanying process of demyelination. Acknowledgment: This research was supported by the SRNSF Georgia RF17_534 grant.

Keywords : myelin basic protein, astrocytes, methyl cycle metabolites, homocysteine, oligodendrocytes
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