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Citrullinated Myelin Basic Protein Mediated Inflammation in Astrocytes

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Abstract : Purpose: During demyelinating inflammatory diseases and after the damage of the myelin sheet, myelin-derived proteins, including myelin basic protein (MBP), are secreted into the extracellular space. MBP shows extensive post-translational modifications, including the deimination of arginine residues. Deiminated MBP is structurally less ordered, susceptible to proteolytic attack, and more immunogenic than the unmodified one. It is hypothesized that MBP could change the inflammatory response in astrocytes. Methods: MBP was isolated and purified from bovine brain white matter. Primary astrocyte cultures were prepared from whole brains of 2-day-old Wistar rats. For evaluation of glutamate uptake/release in astrocytes following treatment of cells with MBP charge isomers, Glutamate Assay Kit was used. The expression of EAAT-2 (excitatory amino acid transporters), peroxisome proliferator-activated receptor gamma (PPAR- γ), inhibitor of nuclear factor kappa B (IkB), and high mobility group protein B1 (HMGB1) in astrocytes were assayed by Western Blot analysis. Results: This study investigated the action of deiminated isomer (C8) on the cultured primary astrocytes and compared its effects with the effects of unmodified C1 isomers. The study found that C8 and C1 MBP differently act on the uptake and release of glutamate in astrocytes: nonmodified C1 MBP increases the uptake of glutamate and does not change the release, whereas C8 decreases the release of glutamate but does not alter the uptake. Nevertheless, both isomers increased the expression of PPAR-γ and EAAT2 in the same intensity. However, immunostaining and Western Blots of cell lysates showed a decrease of IkB and increased expression of HMGB1 after the treatment of astrocytes by C8. Moreover, in the presence of C8, astrocytes release more nitric oxide than unmodified C1 isomers. Conclusion: These data suggest that the deiminated isomer of MBP evokes an inflammatory response and enhances the ability of astrocytes to release proinflammatory mediators through activation of NF-kB after the breakdown of myelin sheets. Acknowledgment: This research was supported by the SRNSF Georgia RF17_534 grant.

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