Sex differences in neurosteroidogenesis in multiple sclerosis pathology

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Research question and background

Multiple sclerosis is a demyelinating neuroinflammatory disease of the central nervous system, characterized by a profound sex difference in prevalence and course. Neurosteroids influence neuroinflammation and remyelination, are neuroprotective and show gender specific regulation. Therefore, we investigated neurosteroid synthesis and expression of neurosteroid receptors along with pro-inflammatory cytokines (e.g tumor necrosis factor-α, interleukin-1β and -6) in normal-appearing white matter and multiple sclerosis lesions of male and female patients (n=21).

Methods and tissues used

Expression of neurosteroid synthetic enzymes, hormone receptors and the pro-inflammatory cytokines tumor necrosis factor-α (TNF-α), interleukin-1β and -6 was quantified by qPCR and immunohistochemistry on paraffin embedded samples of chronic active, inactive lesion and normal appearing white matter. The influence of cytokines on neurosteroid synthesis and signaling was tested on human primary glial cell cultures. Frozen, paraffin embedded and fresh tissue used for primary glia cell isolation was provided by the Netherlands Brain Bank.

Results and conclusion

Sex differences in MS lesions were observed. Males expressed more aromatase (estrogen synthethic enzyme), estrogen receptor β (ERβ) and TNF-α. Females expressed more 3β-hydroxysteroid-dehydrogenase (HDS3B; progesterone synthetic enzyme) and progesterone receptor (PGR). In NAWM, female MS patients showed higher expression of HDS3B and PGR than males. Immunohistochemistry demonstrated neurosteroidogenic enzymes and hormone receptors, mainly in reactive astrocytes in the rim and center of MS lesions. Quantification confirmed increased expression of aromatase in male, and HDS3B in female MS lesions. In female NAWM, HDS3B was seen in astrocytes, and PGR in oligodendrocyte-like cells. Interestingly, aromatase and estrogen receptor-α (ERα) mRNA levels were positively correlated with that of TNF-α. In primary cultures of human microglia and astrocytes, TNF-α caused increased ERα expression suggesting that estrogen signaling increases in response to inflammatory signals.

In conclusion in male MS lesions, estrogen synthesis and ERβ-mediated signaling are induced, whereas in female MS lesions and NAWM progestagen synthesis and signaling are induced. These differences may account for sex differences in multiple sclerosis prevalence and course.