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White matter reactive astrocytes express nuclear estrogen receptor alpha (ESR1) in experimental autoimmune encephalomyelitis and multiple sclerosis

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The mechanism of action of estrogens as modulators of inflammation and neuroprotection in neurodegenerative disorders is a matter of great debate. Whereas an active astrocytic involvement in the physiopathology of neurodegenerative or neuroinflammatory disorders has now emerged, the glial expression pattern of estrogen receptors (ER) in multiple sclerosis (MS) and its animal model, experimental autoimmune encephalomyelitis (EAE) remains undefined.

We found that nuclear ERalpha is expressed by reactive astrocytes in the white matter cord during chronic EAE in mice, and that estradiol treatment after EAE onset alleviated ongoing EAE symptoms and was associated in the spinal cord white matter with a reduction of astroglial reactivity, leukocytic infiltration and axonal loss. In order to investigate the astrocytic expression of ERalpha in MS, archival paraffin sections from frontal cortex of secondary progressive MS patients and control subjects were used for double immunocytochemistry. ERalpha was hardly detected in the white matter tracts of control subjects, or around blood vessels where increased GFAP staining was observed in control subject 1 (Wegener case). In the grey matter, moderate ERalpha immunoreactivy in astrocytic fibers could be observed in layer I, particularly for astrocytes contacting dilated blood vessels in control subject 1. Otherwise, cortical astrocytes with several processes and in close proximity to blood vessels were not stained for ERalpha in control and MS subjects. In the normal appearing white matter of MS patients, astrocytes expressed relatively low levels of extranuclear ERalpha compared to those in the white matter at the rim of chronic plaques (identified by the lack of Sudan black staining). In contrast, reactive astrocytes in the demyelinating white matter (as assessed by lower Sudan black staining and CD68 immunoreactivity on adjacent sections) exhibited nuclear ERalpha staining whereas ERalpha was not evidenced in chronic plaques though dense GFAP immunoreactive fibers were detected.

Herein, we show for the first time that ERalpha is expressed by reactive astrocytes in MS white matter, with a nuclear staining that could be only observed in demyelinating lesions. These data support white matter astroglia cells as an important direct target for estrogen anti-inflammatory actions in MS.