Astrocytic NR1D1 Signaling in aging and Amyotrophic Lateral Sclerosis

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Neuroinflammation is linked to the aging process and contributes to the progression of neurodegenerative diseases. Astrocytes play a key role in the regulation of the innate immune response in the central nervous system. NR1D1 is a member of the nuclear receptor superfamily and it is an essential component of the molecular clock. It functions as a transcriptional repressor and is considered a key regulator of fatty acid-binding protein 7 (FABP7) expression, a protein that is upregulated by astrocytes in multiple pathological conditions, including Alzheimer's disease and amyotrophic lateral sclerosis (ALS). Accordingly, we previously showed that in astrocyte cultures, silencing NR1D1 increases the expression of FABP7, while the overexpression of FABP7 induces a pro-inflammatory phenotype. Here we investigate a potential role for dysregulated NR1D1 signaling in the modulation of neuroinflammation during aging and ALS. We observed decreased NR1D1 expression in the cerebral cortex of 2-year-old mice, when compared to young 3-month-old animals. This decrease in NR1D1 expression was observed in astrocytes and neurons. In addition, we observed that FABP7 expression increases in a subpopulation of astrocytes in the aging brain. Moreover, astrocytes expressing high FABP7 levels also displayed higher expression of the inflammatory markers, NOS2 and COX2. Decreased NR1D1 expression was also observed in ALS mouse models. Remarkably, NR1D1 overexpression specifically in astrocytes significantly delays disease progression in $SOD1^{G93A}$ mice, a widely used ALS mouse model. Together, our results suggest NR1D1 could play a role in the regulation of astrocyte-mediated neuroinflammation during aging and constitutes a potential therapeutic target in ALS.

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