

## Estradiol control of brain inflammation and pyroptosis

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Stroke and traumatic brain injury (TBI) result in a rapid loss of neurons in the epicenter of the lesion. These initial neuropathological responses are followed by sustained deficiencies in nutrition and oxygenation, ROS and lipid peroxidation with unmanageable spreading of brain destruction. The secondary neuropathological processes depend on escalating neuroinflammation involving the interaction of immune cells including local cells. Irrespective of the disease mechanisms, new insights into the sequence of inflammatory cascades have broadened the knowledge about inflammatory processes and included the inflammasome concept. Inflammasomes are strictly regulated cytosolic protein complexes, act as intracellular sensors of toxic signals and activate pro-inflammatory caspases which then cleave the precursors of pro-inflammatory cytokines into their active forms. Inflammasomes show a large degree of structural heterogeneity due to their protein composition and assembly. They have three main components, a cytosolic pattern-recognition receptor, the enzyme caspase 1 and an adaptor protein that facilitates the interaction between the two. The inflammasomes NLRP1, NLRP3, and AIM2 have attracted strong attention in neuroscience and are in the focus of the present study.

Using transient middle cerebral artery occlusion (tMCAO, male rats) as stroke model, we demonstrate the induction of the inflammasome genes NLRP1, NLRP3 and AIM2 after a delay of several hours with consistent expression profiles of IL1 $\beta$  and IL18. Microglia and neurons mainly stained positive for NLRP1 and ASC. In a related acute rat spinal cord injury model, we confirmed the above results and showed at approx. 3 h post-insult a massive induction of the above inflammasomes. In both experimental models, continuous administration of 17 $\beta$ -estradiol (E2) after the insult reduced the infarct volume and spinal cord lesion. E2 also attenuated the expression of the mentioned inflammasomes and cytokines at the gene level in a dose-dependent way. In addition, E2 regulated a set of regulatory miRNAs known to be involved in the control of immune-modulatory genes.

Our data show that inflammasomes and related miRNA clusters are a critical intracellular platform of neuroinflammation in acute brain damage. Different cell types are involved in inciting and maintaining neuroinflammatory processes. E2 effectively dampened inflammatory processes and inflammasome activation in both disease models.

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