**Neurodegeneration after brain ischemia in aged mice: beneficial effects of Montelukast**

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**Introduction and Aim**. Inflammatory processes are involved in aging and in chronic neurodegenerative diseases. Consequently, anti-inflammatory interventions have been proposed for treatment and/or prevention of age-related diseases. Targets for potential anti-inflammatory drugs could be the pathways of the classical lipid mediators of inflammation, such as the cysteinyl-leukotrienes (Cys-LTs). In particular, montelukast, a Cys-LT receptor antagonist developed to treat asthma, has been shown to restore learning and memory in aged rats, with a reduction in neuroinflammation. Our previous study showed that treatment with montelukast improves fiber re-organization and long-term functional recovery in young brain ischemic mice, reduces inflammation and shifts microglia towards pro-regenerative phenotype. The aim of this study is to investigate the effects of montelukast in ischemic aged mice.

**Methods**. 17-month-old mice were subjected to permanent middle cerebral artery occlusion (pMCAo), and starting from 4.5 hours after pMCAo were treated daily by oral gavage with montelukast (10 mg/kg/day; n=7) or vehicle (n=7). The effects of montelukast treatment on the evolution of infarct size were investigated up to 48 hours using in vivo magnetic resonance imaging (MRI). The motor balance and coordination were assessed in ischemic pMCAo mice and sham-operated mice by balance beam test (BBT) and rotarod test. The cerebral gene expression for inflammatory parameters was evaluated by PCR analysis in mice sacrificed 24 hours after pMCAo, while the microglial phenotype was investigated at 72 hours after pMCAo by immunohistochemistry analysis.

**Results and conclusion**. Although no difference in infarct size and brain damage evolution was observed between vehicle- and montelukast-treated pMCAo mice, montelukast administration significantly improved motor coordination performance compared with vehicle-treated mice ($p<0.05$) at 72 hours after pMCAo both in BBT and rotarod test. Furthermore, montelukast significantly decreased the mRNA expression of the pro-inflammatory mediators Cox2, Il1b, Cxcl10 and Ccl2 compared to vehicle-treated pMCAo mice. Immunohistochemical analysis showed a relevant decrease in the number of CD68+/Iba1+ polarized microglia at the border of the ischemic lesion in montelukast-treated compared to vehicle-treated mice, while no difference was observed in TREM2+/Iba1 cells, indicating a reduction of the pro-inflammatory state of microglia. This study suggests that the Cys-LT signalling is a promising target for developing new, effective therapeutic strategies for stroke in aged patients.