IMPROVEMENT OF FIBER CONNECTIVITY AND FUNCTIONAL RECOVERY AFTER STROKE BY MONTELUKAST, AN AVAILABLE AND SAFE ANTI-ASTHMATIC DRUG

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Introduction: Stroke is one of the main causes of death, neurological dysfunctions or disability in the elderly. Neuroprotective drugs proposed to improve long-term recovery after stroke have unfortunately failed to reach clinical effectiveness. Thus, it has been suggested that restorative therapies should combine neuroprotection and remyelination. Montelukast, an anti-asthmatic drug, was shown to exert neuroprotection in animal models of CNS injuries, but its ability to affect oligodendrocytes (the myelin producing cells) in restoring fiber connectivity, remains to be determined.

Materials and methods: In this study, male CD1mice were subjected to permanent middle cerebral artery occlusion (pMCAo) and treated with montelukast or vehicle for 8weeks. Sham-operated mice were used as control. During the follow up period, mice were weekly subjected to *in vivo* magnetic resonance imaging and electrophysiological analyses in order to evaluate damage evolution and functional outcome, respectively. At the end of experimental protocol, *ex vivo* diffusion tensor imaging (DTI)-based fiber tracking and immunohistochemistry were performed to measure white matter integrity and oligodendrocyte injury. Reporter GPR17iCreERT2:CAG-eGreen florescent protein (GFP) mice were used to assess the involvement and trace the destiny of oligodendrocyte precursor cells (OPCs) in ischemic brain remodeling after drug-treatment.

Results: In parallel with a reduced evolution of ischemic lesion and atrophy, montelukast increased DTI-derived axial diffusivity and myelin fibers number, the density of myelin basic protein (MBP) and the number of GSTpi+ mature oligodendrocytes. Important, Montelukast also rescued MCAo-induced impairment of local field potentials in ischemic cortex, suggesting improved fibers reorganization and connectivity. Then, to ascertain whether these effects involved changes of OPCs activation and maturation, we used reporter GPR17iCreERT2:CAG-eGreen GFP mice to trace the fate of OPCs throughout animal's life. Our results showed that montelukast enhanced OPC recruitment and proliferation at acute phase (2weeks after pMCAo), and increased their differentiation to mature oligodendrocytes at chronic phase of brain ischemia (8weeks after pMCAo). Considering that a crosstalk between OPCs and microglia has been widely reported in the context of demyelinating insults, we also assessed microglia activation. We observed that montelukast influenced the phenotype of microglial cells by increasing the number of beneficial M2polarized microglia/macrophages, over the detrimental M1phenotype at acute phases of brain ischemia (3days after pMCAo).

Discussion and conclusion: We demonstrated that montelukast improves fiber re-organization and long-term functional recovery after brain ischemia, enhancing recruitment and maturation of OPCs. The present data suggest that montelukast, an already approved drug, could be "repositioned" as a protective drug in stroke acting also on fiber re-organization and brain connectivity.