The project goal and its significance

Multiple sclerosis is an autoinflammatory and neurodegenerative disease that affects the brain and spinal cord. It is the leading cause of non-traumatic neurological disability in young adults in the world. In multiple sclerosis, the lipid sheaths (myelin) that insulate neuronal axons are attacked and destroyed by the immune system. The loss of myelin leads to axonal degeneration and neuronal cell death. In recent years there has been an increase in disease-modifying therapies for the most common, relapsing-remitting, form of multiple sclerosis. There are currently nearly 30 therapies available for treatment. The disease-modifying therapies do not cure multiple sclerosis but significantly slow down its progression and substantially enhance the quality of life. These therapies modify the immune system to reduce the number and severity of relapses (temporary exacerbations of the disease) but have very limited effect on myelin repair (remyelination) or neuronal protection. There are no remyelination or neuroprotective therapies available.

Reasons for attempting this particular research topic

We have identified a receptor called EBI2 capable of regulating myelination in mice. Our research to date showed that (i) the EBI2 receptor plays a role in normal myelin development after birth in mice, (ii) is necessary for remyelination under pathophysiological conditions in mouse brain slices and, (iii) is needed for remyelination in a mouse model of multiple sclerosis. This project aims to build on these findings and investigate the remyelinating properties of the natural ligand of the EBI2 receptor, the oxysterol 7α,25OHC, in the mouse model of multiple sclerosis, the cuprizone model. The ultimate goal of this project is to find a novel remyelination-stimulating therapy.

Description of research

To reach our goals we will treat mice that underwent demyelination with the EBI2 ligand, the oxysterol 7α,25OHC and compare the level of remyelination in these mice to the untreated animals. We will also examine the molecular and cellular mechanisms that regulate EBI2/7α,25OHC-mediated remyelination (myelin repair) in specific central nervous system cells (oligodendrocytes, astrocytes and microglia) and mouse brain slices. This will allow us to better understand the processes involved in remyelination and the role of EBI2/7α,25OHC.

Expected results

We expect that mice treated with 7α,25OHC in the mouse model of multiple sclerosis will remyelinate (repair myelin) more efficiently than the non-treated mice. Activation of EBI2 with 7α,25OHC will induce specific molecular and cellular mechanisms in the central nervous system cells and the brain slices and these mechanisms will be modulated with the EBI2 ligand.

Research impact

The successful completion of this project will bring closer the creation of the first remyelinating therapy for humans.