PSYCHOSTIMULANT INDUCED-NEUROINFLAMMATION: CLARIFYING THE ASTROCYTE-MICROGLIA CROSSTALK UNDER IL-10, AN IN VITRO STUDY

Introduction

Methamphetamine (Meth) is an illegal and potent psychostimulant drug that is highly addictive and commonly associated with serious co-morbidities and high mortality. Hallmarks of Meth addiction are characterized by the disruption of the dopaminergic system, concomitant with terminal degeneration and eventual neuronal death. However, Meth has been increasingly recognized to cause the release of inflammatory mediators.

Microglia are a class of brain immune-regulator cells that are essential for the well-functioning of the central nervous system. The functions of microglia are stimulation-dependent and strongly impact the cells that surround them. Pro-inflammatory cytokines like IFN-gamma and TNF are responsible for turning microglia into a reactive state, leading to increased production of iNOS and ROS and release of pro-inflammatory molecules. However, in the presence of anti-inflammatory cytokines, like IL-4 or IL-10, microglia presents a more anti-inflammatory profile, that is neuroprotective and promotes tissue repairing. The neuronal damage, cognitive impairments and neuroinflammation caused by Meth exposure may be related to an immunedysregulation that leads to changes in the secretion of chemokines and cytokines, like TNF, IL-1beta and IL-6.

Recently, we have successfully demonstrated that microglia activation under Meth-exposure, depends on astrocytic release of glutamate and TNF. We have also established that Meth induces neuronal remodeling, affecting both neuronal ramifications and dendritic spines, which can also be linked to Meth induced neuroinflammation. Thus, interventions that aim at reducing inflammation may be useful in treating Meth use disorders. Importantly, IL-10 seems to counterbalance damage driven by excessive neuroinflammation and can therefore be protective in several conditions. Our preliminary data indicates that IL-10 presents a protective in vivo effect in mice exposed to Meth, and we are, therefore, interested in further explore the mechanisms involved.

Aim

Unravel the signaling mechanisms modulating the protective role of IL-10 in microglia activation under Meth-exposure.

Methodology

- **IL-10** (10ng/ml)
- **100 μM Meth**
- **ACM at 24h**

Evaluations in astrocytes

- Release of Glutamate (FLIPE probe for FRET)
- Protein levels by ELISA and mRNA levels by PCR for TNF

Evaluations in microglia

- Protein levels of iNOS, ROS and arginase by immunocytochemistry
- Protein levels of IL-1beta and IL-6 by ELISA
- mRNA levels of IL-1beta, IL-6, TNF-alpha and iNOS by PCR
- Beads for the assessment of phagocytosis

Conclusion

Substance abuse is a worldwide health problem that has increased its prevalence in the latest years. Because treatments presently available are not directed to psychostimulants, new therapeutic strategies are highly valuable. We expect that this study will bring new insights on how Methamphetamine affects the crosstalk between different brain cells and how IL-10 can contribute to an innovative strategies for substance abuse disorders.

References