Inflammation and epilepsy: the contribution of astrocytes
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AIM AND OUTLINE OF THE THESIS

In the last two decades increasing research has been focused on the role of astrocytes in brain physiology and pathology: astrocytes were shown to be actively involved in neuronal communication and homeostasis. The contribution of inflammation in epilepsy and epileptogenesis has pointed to astrocytes as key components of this condition characterized by hyperexcitability of the neural tissue. In fact astrocytes represent an important source of immunologically relevant cytokines and chemokines which have been demonstrated to increase neuronal excitability in different experimental models. As almost 30% of epileptic patients are pharmacoresistant, understanding the role of astrocytes in the pathology could provide new targets for the development of alternative treatments for these forms of epilepsy. The general aim of this thesis was to investigate the contribution of astrocytes to epilepsy in order to gain more insight into the pathways involved in the etiopathogenesis of this disease. The specific objectives included: a) investigation of inflammatory pathways and epilepsy; b) study of mechanisms of regulation of the inflammation; and c) evaluation of the involvement of astrocytes in neuronal signaling. We used a variety of approaches, including the study of human material, animal models and in vitro systems aiming to contribute to the elucidation of mechanisms underlying untreatable epilepsy, in an attempt to find new molecular targets for therapy.

After a general introduction on the physiopathology of astrocyte in relation to epilepsy (chapter 1.1), in chapter 1.2 we reviewed current evidence regarding the role of astrocytes in the regulation of the innate immune responses in epilepsy. In chapter 2.1 we evaluated the expression and the cellular distribution of tPA and uPA in several epileptogenic pathologies. In chapter 2.2 we studied the activation of inflammatory pathways in FCD type I and II focusing on the inflammatory cell components and the induction of major proinflammatory pathways and molecules. In chapter 2.3 we investigated the expression and cellular distribution of toll-like receptors (TLRs) 2 and 4, and of the receptor for advanced glycation end products (RAGE), and their endogenous ligand high-mobility group box 1 (HMGB1), in epilepsy associated with focal malformations of cortical development. The acute effect of two proinflammatory molecules (IL-1β and HMGB1) on neuronal excitability in relation with activation of astrocytes was studied in chapter 2.4. In chapter 2.5 we examined the expression pattern of an astrocytic potassium inward rectifier channels (Kir) 4.1 in relation to epilepsy and inflammation. Further we investigated the expression and cellular distribution of miRNA-146a (miR-146a) in a rat model of TLE as well as in human TLE (chapter 3.1), in epilepsy-associated glioneuronal lesions and in cultured astrocytes (chapter 3.2). In chapter 4.1 we evaluated the expression pattern and distribution of cannabinoid receptors in nor-
mal human development as well as in patients with malformations of cortical development (MCD). Further, we focused on the expression pattern and distribution of ADK, primarily present in astrocytes, in a rat model of TLE and in human TLE (chapter 4.2) as well as in human astrocytic tumors related to epilepsy (chapter 4.3). Finally in chapter 5 we discussed the significance of our results and contextualized our findings in relation to the state of the art.