Inflammation and epilepsy: the contribution of astrocytes
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SUMMARY

Neurons are not the only cell type in the central nervous system (CNS). In fact they are outnumbered by different non neuronal cells, collectively called glia. For a long time, it was believed that glial cells only functioned as structural and trophic support for neurons, rather than actually contributing to network activity. However, recently they were found to have numerous important functions that allow them to be closely involved in neuronal signaling. Moreover astrocytes represent an important source of immunologically relevant cytokines and chemokines, and reactive astrogliosis (a process of activation of astrocytes) is a pathological hallmark of various types of medically refractory focal epilepsy. The activation of inflammatory pathways and the consequent release of inflammatory molecules by astrocytes can alter neural network excitability via induction of various mechanisms, with either direct or indirect impact on neuronal functions.

In this thesis we investigate the contribution of astrocytes to epilepsy in order to gain more insight into the pathways involved in the etiopathogenesis of this disease. The thesis is divided in the following chapters: Introduction, Inflammatory pathways and epilepsy, Regulation of inflammation in astrocytes: the role of miR 146a, Astrocytes mediated signaling and epilepsy, General Discussion. Chapter 1.1 is a general introduction on astrocytes physiology and their dysfunctions in epilepsy and in chapter 1.2 we review the current evidence regarding the role of astrocytes in the regulation of the innate immune responses in epilepsy. In chapter 2 we investigate some of the inflammatory pathways that could contribute to epilepsy. In particular in chapter 2.1 we show that tissue plasminogen activator (tPA), urokinase plasminogen activator (uPA) and uPA receptor are upregulated in human hippocampal sclerosis (HS) specimens and in a model of rat temporal lobe epilepsy (TLE). In chapter 2.2 we demonstrate that focal cortical dysplasia (FCD) I and II, even though they have a comparable history of seizures, are characterized by different activation of inflammatory processes, suggesting a specific role of inflammation on seizure generation, rather than it being a consequence of the seizure activity. In chapter 2.3 we show that the inflammatory pathway HMGB1-TLRs/RAGE (already shown to be involved in epilepsy) is upregulated in tissue from patients affected by different types of MCD associated with epilepsy. In chapter 2.4 we observe a pro-epileptic effect of the proinflammatory molecules HMGB1 and IL-1β in a model of focal epilepsy in acute brain slices from rats. Further we showed that chronic exposure to IL-1β can induce a decrease of the expression of Kir 4.1 in cultured astrocytes (chapter 2.5). In chapter 3 we study a mechanism of regulation of inflammation occurring in astrocytes in epileptic patients and in rat TLE. In chapter 3.1 we show a strong upregulation of mir146a in the astrocytes of both human and rat TLE. We then moved to an in vitro system where we can modulate the expression of mir146a in cultured astrocytes showing that its upregula-
tion can decrease the IL-1β signaling and the inflammatory markers IL-6 and COX2 (chapter 3.2). In chapter 4 we show different pathways that are involved in the astrocytes-mediated signaling in relation to epilepsy. In particular in chapter 4.1 we study the distribution pattern of cannabinoids receptors (CBRs) during the normal brain development and we show a strong upregulation of both CBRs in MCD associated with epilepsy, in different cellular types. We further investigate the adenosine kinase (ADK) levels in epilepsy showing a prominent upregulation in tissue from epileptic patients and from experimental rat model of TLE (chapter 4.2). Moreover we demonstrate that astrocytes from epilepsy-associated tumors have an increased expression of ADK, in comparison to tumors without epilepsy (chapter 4.3). Finally, in chapter 5 we discuss our findings from patient studies and experimental models proposing that the activation of specific proinflammatory pathways in astrocytes could contribute to neuronal activity and synchronization thus promoting epileptical activity.