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Review article

Nonsteroidal anti-inflammatory drugs in clinical and experimental epilepsy

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SUMMARY

Current antiepileptic drugs have limited efficacy and provide little or no benefits in 30% of the patients. Given that a role for brain inflammation in epilepsy has been repeatedly reported in recent years, the potential of anti-inflammatory drugs should be explored in depth, as they may provide new therapeutical approaches in preventing or reducing epileptogenesis. Here, we review preclinical (both *in vivo* and *in vitro*) and clinical epilepsy studies in which nonsteroidal antiinflammatory drugs (NSAIDs), i.e. cyclooxygenase-2 (COX-2) selective inhibitors (COXIBs) and nonselective NSAIDs, were used for seizure control. The effects of NSAIDs are reviewed in animal models of both chemical (pilocarpine, kainic acid, pentylenetetrazol, or carbachol administration) and electrical (tetanic hippocampal stimulation, electroshock) seizure induction. In the pilocarpine model, NSAIDs are neuroprotective, reduce mossy fiber sprouting or diminish *P*-glycoprotein upregulation, but only rarely protect against seizures. While neuroprotective effects have also been observed in the kainic acid model, NSAIDs tend in general to worsen seizure activity. Effects of COXIB administration in the pentylenetetrazol-induced seizures model are variable, alternating from protection against seizures to null effects or even increased incidence of convulsions. Moreover, NSAIDs tested in the tetanic hippocampal stimulation model diminished the seizure-associated *P*-glycoprotein upregulation, but were not very effective in seizure control. NSAIDs efficacy in experimental *in vivo* epilepsy studies may be influenced by multiple factors, including the timing of administration (before or after *status epilepticus* induction), the animal model of epilepsy or some of the signaling pathways involved in cyclooxygenase induction (e.g. prostaglandins and their receptors). On the other hand, the few clinical studies on the use of NSAIDs in neurological pathologies accompanied/characterized by seizures indicate that nonselective NSAIDs (e.g. aspirin) in prolonged, low-dose treatments may offer protection against seizures and stroke-like events. No clinical trials in epileptic patients using COXIBs have been conducted so far, as several international drug-control authorities have withdrawn these drugs from the market; future studies should focus on improved COXIB formulations. We argue that, while the available evidence is still inconclusive, the potential therapeutic benefits of controlling and diminishing brain inflammation in the treatment of epilepsy should be actively explored.

Contents

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1. Introduction

Epilepsy affects 50 million people worldwide according to the World Health Organization and 20–30% of patients develop resistance to antiepileptic drugs. The side effects of antiepileptic treatments represent a heavy economic burden (de Kinderen et al., 2014) and have a significantly negative impact on the quality of life (Luoni et al., 2011).

Although the standard approach to understand, diagnose, and treat epilepsy revolves around neuronal mechanisms leading to hypersynchronous firing, recent experimental studies have highlighted the essential role played by cellular and molecular brain inflammatory mechanisms in the pathogenesis of epilepsy. These include astrogliosis, neuroinflammation, vascular inflammation, microglial activation, brain microvascular endothelial cells alterations, blood brain barrier (BBB) leakage, recruitment of inflammatory cells, leukocyte-endothelial adhesion changes, angiogenesis, etc. (Dubé et al., 2006; Fabene et al., 2008; Ravizza et al., 2011; Vezzani et al., 2011; Friedman and Dingledine, 2011; Aronica et al., 2012; Dedeurwaerdere et al., 2012; Vezzani et al., 2013; Fabene et al., 2013; Bertini et al., 2013; Radu et al., 2013; Benson et al., 2015). In particular, the IL-1 receptor/Toll-like receptor, cyclooxygenase (COX)-2, and TGF-β signaling pathways have been found to mediate the dysfunctions induced by brain inflammation in epilepsy (Vezzani et al., 2013). Several pieces of evidence support the involvement in epileptogenesis of inflammatory mediators, released by peripheral immune cells and by the cellular components of the so-called neurovascular unit (NVU), an integrated signaling system that includes endothelial cells, pericytes, astrocytes, microglia, and neurons (Hawkins and Davis, 2005; Fabene et al., 2010; Vezzani et al., 2011; Fabene et al., 2013; Bertini et al., 2013; Radu et al., 2013; Muoio et al., 2014; Tran and Gordon, 2015; Barakat and Redzic, 2016).

Moreover, clinical studies have indicated the involvement of the brain inflammatory response in human epilepsy, including autoimmune encephalitis, and significant efforts are being devoted to the identification of epilepsy-associated inflammatory biomarkers in the cerebrospinal fluid and serum of affected patients (Pardo et al., 2004; Bauer and Bien, 2009; Aronica and Crino, 2011; Bauer and Bien, 2016).

To date, none of the drugs approved by the U.S. Food and Drug Administration (FDA) as anticonvulsants have demonstrated disease-modifying properties in epilepsy (Varvel et al., 2015). On the other hand, anti-inflammatory therapy may hold promise in this respect (Fabene et al., 2008; Ravizza et al., 2011; Dedeurwaerdere et al., 2012).

Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used in clinical practice as anti-inflammatory, analgesic, and antipyretic agents. In the brain, NSAIDs reduce the inflammatory response by acting on multiple non-neuronal targets of the NVU, e.g. reducing C5a- and CXCL8-induced neutrophil migration (Bertolotto et al., 2014), downregulating L-selectin expression in neutrophils (Gómez-Gaviro et al., 2000), targeting leukocyte-mediated inflammation, independently of prostaglandin production (Angelis-Stoforidis et al., 1998; Ottonello et al., 2009), inhibiting leukocyte adhesion (Díaz-González and Sánchez-Madrid, 1998), contributing to endothelial apoptosis (Liou et al., 2008), and exerting anti-angiogenic effects (Monnier et al., 2005).

In recent years, research into the causes and mechanisms of epilepsy has extended beyond the traditional focus on hypersynchronous neuronal firing to include the role of NVU activation (Fabene et al., 2008; Vezzani et al., 2011; Dedeurwaerdere et al., 2012; Fabene et al., 2013; Bertini et al., 2013; Radu et al., 2013). In this view, it may make sense to target NVU components with anti-inflammatory therapies, in an attempt to induce an overall reduction of neuroinflammation associated to the epileptic condition. Whereas it has been shown that NSAIDs can modulate neuronal firing (Schiller, 2004; Fernández et al., 2010; Huang et al., 2013), several preclinical studies have demonstrated that these drugs can also act on the non-neuronal partners of the NVU, including microglia, astrocytes (Aleong et al., 2003; Ajmone-Cat et al., 2010), endothelial cells (Liou et al., 2008; Solmaz et al., 2012), pericytes (Kennedy-Lydon et al., 2015), and on immune cells (Angelis-Stoforidis et al., 1998; Díaz-González and Sánchez-Madrid, 1998; Ottonello et al., 2009; Bertolotto et al., 2014).

NSAIDs might influence neuronal hyperexcitability in epilepsy by regulating prostaglandins (PGs) and/or their EP receptors, as part of the COX enzymatic signaling pathway. All the above signaling components, together with pro-inflammatory cytokines, have been proposed to take part in a pro-epileptogenic feedback loop (Chen and Bazan, 2005; Cole-Edwards and Bazan, 2005; Fellin et al., 2006; Ding et al., 2007; Jiang et al., 2013; Shimada et al., 2014). Moreover, astrocytic production of PGs involves both neuron-astrocyte and microglia-astrocyte crosstalk, and contributes to neuronal apoptosis (Bezzi et al., 2001a,b).

Additionally, NSAIDs were demonstrated to act on the ATP-binding cassette transporters, including P-glycoprotein (P-gp), in different cell subtypes (Angelini et al., 2008; Yan et al., 2012; Takara et al., 2009). In particular, several studies on experimental seizure models demonstrated that NSAIDs downregulate P-gp expression and activity in brain endothelial cells (Bauer et al., 2008; Zibell et al., 2009; van Vliet et al., 2010; Holtman et al., 2010). Both clinical and experimental epilepsy studies demonstrated that spontaneous recurrent seizures induce alterations of efflux transporter functionality, as well as P-gp upregulation (van Vliet et al., 2004; Hoffmann and Löscher, 2007). The alterations can be associated with decreases in blood-brain barrier permeability to antiepileptic drugs, thus contributing to drug-resistant epilepsy (Ma et al., 2013; Rojas et al., 2014a; Li et al., 2014; Wang et al., 2016). A recent study based on PTZ-induced seizures has shown that brain P-gp overexpression contributes to a progressive seizure-related membrane depolarization in hippocampal and neocortical neurons (Auzmendi