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During a systemic inflammatory response, the effect of non-steroidal anti-inflammatory drugs on seizure susceptibility in the immature brain may depend on the proconvulsant and anticonvulsant mechanisms simultaneously induced by the elevation of parenchymal prostaglandin E_2 levels

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Abstract Clinical evidence from paediatric neurology supports the possibility that a protracted inflammatory state in the central nervous system (CNS) may enhance the predisposition of brain tissue to develop seizures. Consequently, non-steroidal anti-inflammatory drugs (NSAIDs) as well as selective cyclooxygenase-2 (COX-2) inhibitors were expected to positively modulate seizure susceptibility during a systemic inflammatory response. Nevertheless, experimental findings and clinical evidence provide controversial results. As a possible explanation for these apparent discrepancies, it is hypothesised that the amount of prostaglandin E_2 (PGE_2) induced in the immature brain parenchyma during systemic inflammatory response is crucial since PGE_2 plays a dual role. Indeed, on the one hand, this prostaglandin increases seizure susceptibility by stimulation of glutamate release from neurons and astrocytes. On the other hand, however, the same prostaglandin induces a massive release of corticosterone, being this hormone known to inhibit efficiently the seizure susceptibility of the immature brain. Hence, the dose–response curve of any given NSAID/COX-2 inhibitor on seizure susceptibility is expected to show different patterns, depending on the amount of PGE_2 levels produced in the brain parenchyma during the effect of drug. The proposed hypothesis also suggests that mild to moderate increase of PGE_2 levels in the immature brain parenchyma may act as a 'preconditioning' stimulus, i.e., it may confer a transient resistance to develop seizure-induced brain injury, besides to efficiently counteract seizure susceptibility.

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Introduction

Clinical evidence from paediatric neurology supports the possibility that a protracted inflammatory state in the CNS may enhance the predisposition of brain tissue to develop seizures. Indeed, increased serum or brain levels of proinflammatory cytokines and markers of immune system activation have been described in patients with West syndrome [1], tuberous sclerosis [2] and, in particular, Rasmussen's encephalitis [3]. The possibility that proinflammatory mediators may negatively affect seizure susceptibility at young ages deserves attention since the occurrence of an ictal event during an inflammatory response exacerbates seizure-induced injury in the immature brain and increases the likelihood to develop seizures as well as seizure-induced brain injury in adulthood [4–10]. Thus, targeting of proinflammatory mediators affecting seizure susceptibility is nowadays a priority in the pharmacological research for the treatment of convulsive disorders at young (as well as adult) ages. It is well established that prostaglandins and lipoxygenase reaction products are induced in the brain during seizures [11] and these molecules *per se* were shown to increase seizure susceptibility of nervous tissue. In particular, evidence from literature has largely demonstrated that prostaglandin E_2 (PGE_2), the major enzymatic product of cyclooxygenase-2 (COX-2) activity [12], enhances glutamate release from astrocytes and neurons [13,14]. The overall effect is an enhancement of tissue excitability which leads to an increase of likelihood of nervous tissue to generate and propagate seizures. Consequently, the administration of non-steroidal anti-inflammatory drugs (NSAIDs) as well as selective COX-2 inhibitors was expected to positively modulate seizure susceptibility in the experimental models of epilepsy, thus opening the possibility to use these molecules as therapeutic treatment in human epilepsies. Nevertheless, evidence provides controversial results [15]. As it concerns seizure models involving neonatal rodents, Kim and Jang [16] report that inhibition of COX-2 activity by Celecoxib delays seizure onset induced by a proconvulsant agent. Additionally, Heida and colleagues [17] propose an experimental model of febrile seizures by the systemic administration of a mild dose of lipopolysaccharide (LPS, a cell-wall component of Gram-negative bacteria) to 14-day rats. Indeed, seizure susceptibility to a proconvulsant agent was shown to increase during the LPS-induced increment of body temperature (fever), hence the proposal of such experimental conditions as a model of febrile seizures. These findings support the possibility that proinflammatory mediators may enhance the predisposition of brain tissue to develop seizures. Nevertheless, Auvin and colleagues [10] report that a mild dose of systemically administered LPS delays seizure onset in rat pups. Delay is shown statistically significant in 15-day rats, but a similar trend is already observed in 7-day rats.

Aim of the work

The goal of this work is to formulate a conceivable and testable hypothesis to improve the understanding of the effect of systemic inflammation on seizure susceptibility in the immature brain, hence, to better evaluate the possibility to exploit NSAIDs/COX-2 inhibitors as therapeutic molecules in paediatric epilepsies. Speculation is based on evidence from literature and the experimental proposals are all intended to be accomplished by animal models of epilepsy.

Basic considerations

It is worth considering the mechanism by which the inflammatory response in the periphery propagates to the CNS. During systemic inflammation, proinflammatory cytokines released into the bloodstream stimulate endothelial cells at the blood–brain-barrier to induce the transcription of genes of proinflammatory mediators such as the one encoding COX-2. The subsequent PGE_2 production by the entire cerebral vasculature was shown to play a critical role in initiating the parenchymal microglia and neurons responses as well as the neurophysiological outcomes that take place during immunogenic stimuli. These include sickness behaviour, fever and, importantly, activation of the hypothalamic–pituitary–adrenal (HPA) axis [18,19]. A proinflammatory stimulus such as LPS is often used as an inducer of experimental systemic inflammation. Accordingly, LPS potently activates HPA axis in rat pups, besides in adults [20,21], by triggering PGE_2 production in the brain parenchyma [22–24] thus inducing a massive release of corticosterone into the bloodstream. Circulating corticosterone enters the brain and act on two cognate receptor subtypes, namely mineralocorticoid (high affinity receptor, a.k.a. type I) and glucocorticoid (low affinity receptor, a.k.a. type II). In the immature brain, mineralocorticoid receptors are more abundant than glucocorticoid receptors and, importantly, they were shown to significantly counteract seizure susceptibility [25–27]. This effect was shown age-dependent since appeared effective within the first four–five weeks of postnatal life. Interestingly, the anticonvulsant property mediated by agonists to mineralocorticoid receptor, including corticosterone, has a short latency of occurrence (within 15 min or less, depending on the agonist used) so that to exclude a genomic effect by binding to nuclear receptors, hence suggesting an involvement of membrane mineralocorticoid receptors. These receptors mediate non-genomic actions of corticosteroids [28,29] and they were shown developmentally regulated [30].

The hypothesis

The aforementioned evidence suggests that PGE_2 plays a dual role in the modulation of seizure susceptibility in the immature brain. On the one hand, PGE_2 activates the HPA axis thus leading to an anticonvulsant effect mediated by corticosterone acting on membrane mineralocorticoid receptors. On the other hand, PGE_2 *per se* enhances seizure susceptibility (Fig. 1). It is conceivable that, as long as the levels of parenchymal PGE_2 induced by a systemic inflammation are moderately increased, the anticonvulsant effect mediated by membrane mineralocorticoid receptors prevails over an enhancement of seizure susceptibility induced by the raise of PGE_2 levels. Therefore, the effect of