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The COX-2/prostanoid signaling cascades in seizure disorders

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Abstract

Introduction—A robust neuroinflammatory response is a prevalent feature of multiple neurological disorders, including epilepsy and acute status epilepticus. One component of this neuroinflammatory reaction is the induction of cyclooxygenase-2 (COX-2), synthesis of several prostaglandins and endocannabinoid metabolites, and subsequent activation of prostaglandin and related receptors. Neuroinflammation mediated by COX-2 and its downstream effectors has received considerable attention as a potential target class to ameliorate the deleterious consequences of neurological injury.

Area covered—Here we describe the roles of COX-2 as a major inflammatory mediator. In addition, we discuss the receptors for prostanoids PGE_2, PGD_2, and $PGF_{2\alpha}$ as potential therapeutic targets for inflammation-driven diseases. The consequences of prostanoid receptor activation after seizure activity are discussed with an emphasis on the utilization of small molecules to modulate prostanoid receptor activity.

Expert opinion—Limited clinical trial experience is supportive but not definitive for a role of the COX signaling cascade in epileptogenesis. The cardiotoxicity associated with chronic coxib use, and the expectation that COX-2 inhibition will influence the levels of endocannabinoids, leukotrienes and lipoxins as well as the prostaglandins and their endocannabinoid metabolite analogs, is shifting attention towards downstream synthases and receptors that mediate inflammation in the brain.

Keywords

cyclooxygenase-2; endocannabinoid; EP1; EP2; epileptogenesis; NSAID; prostaglandins; seizures; epilepsy

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Declaration of interest

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1. Introduction

Sterile inflammation involves a multi-pronged process by which the body responds to injury or severe over-use. In the brain, inflammation can be initiated by prolonged seizures, infections (e.g., neurocysticercosis), tumors, autoimmune disorders and other strong risk factors for the development of epilepsy. Major inflammatory drivers in the brain include COX-2, IL-1β, TNF-α, TGF-β and CCL2 (Table 1). Inflammatory signaling can lower the seizure threshold, and in turn epilepsy in mouse and man is associated with neuroinflammation (1, 2). Here we focus on one of the major inflammatory signaling cascades in the brain, that mediated by the cyclooxygenases.

2. Cyclooxygenase-2 as a major inflammatory mediator

Cyclooxygenase-2 (COX-2) has been widely explored as a biological target for the development of anti-inflammatory and pain medications (3–5). Unlike constitutively expressed cyclooxygenase-1 (COX-1), which is required for physiological and homeostatic functions (6, 7), COX-2 is usually present at low levels but is induced at sites of injury, surgery, seizures or an infection. COX-2 is a key driver of inflammation and pain in a variety of peripheral diseases including rheumatoid arthritis, chronic obstructive pulmonary disease, inflammatory bowel disease (8–11), and various manifestations of cancer (12, 13). A significant body of literature indicates that COX-2 is also upregulated in injury-related CNS disorders such as traumatic brain injury (14), ischemic stroke and seizures (15–17). COX-2 is also constitutively expressed in kidney and some brain neurons, and it regulates natriuresis, diuresis and vasodilation (18, 19). Several pharmaceutical companies discovered and developed small molecule inhibitors of COX-2, namely rofecoxib (Vioxx), valdecoxib (Bextra) and celecoxib (Celebrex), to treat pain and inflammatory osteoarthritis or rheumatoid arthritis. Chronic use of highly selective COX-2 drugs in arthritis patients resulted in severe cardiovascular effects including heart attack and stroke. As a result, Vioxx and Bextra have been withdrawn from the market since 2004 (20). A less-selective COX-2 drug, Celebrex, is still in clinical use with a black-box warning for increased risk for cardiovascular events and gastrointestinal bleeding.

COX-2 promotes inflammation in part through the synthesis of prostaglandins from arachidonic acid (21). First, it catalyzes the conversion of arachidonic acid to the intermediate prostaglandin-H_2, which is then converted by cell specific synthases to thromboxane-A2 (TxA2) and four different prostaglandins, PGD_2, PGE_2, $PGF_{2\alpha}$, and PGI_2 (prostacyclin), which are collectively termed prostanoids. The rate-limiting factor for the synthesis of a specific prostanoid is the expression level of cell specific prostanoid synthase enzymes. Notably, in brain $PGF_{2\alpha}$ appears to be largely formed by enzymatic conversion from PGE_2. As shown in Figure 1, the prostanoids activate nine G protein-coupled receptors, three of which (EP3, FP, TP) have multiple isoforms (22, 23). These receptors serve specific functions in physiological and pathological conditions, and act mainly via three downstream cell-signaling pathways. DP1, EP2, EP4 and IP mediate smooth muscle relaxation via elevation of cellular cAMP, thus have a role in maintenance of myometrium, postnatal development and cardioprotection, whereas EP1, FP and TP receptors contract smooth muscle via Ca^{2+} mobilization. Activation of EP3 and DP2 receptors reduces cAMP levels

(Figure 1). From findings with gene-knockout models, and small molecule modulators for each of these receptors, it has been proposed that several of these receptors play protective as well as deleterious roles depending on a disease or condition, displaying “yin-yang” characteristics during the evolution of a particular disease (22, 23). Thus, it is very important to preserve the bioactivity and the function of several of these receptors that do not have a pro- inflammatory role, and to selectively target pro-inflammatory receptors at the right time to minimize adverse effects.

COX-2 also metabolizes the two major endocannabinoids to form prostaglandin glycerol esters and ethanolamides, referred to as prostamides (Figure 1), which have both proinflammatory and anti-inflammatory effects (24, 25). PGE_2-EA (prostamide E2) can bind all four PGE_2 receptors but with 500-fold lower potency than PGE_2 itself (26); whether the canonical PGE_2 receptors mediate the effects of PGE_2-EA is unlikely, and with one exception little else is known about receptors for the other prostanoid analogs. The discovery of selective prostamide-$F_{2\alpha}$ agonists and antagonists led to the postulate of an independent receptor for this endocannabinoid metabolite, and indeed a heteromeric receptor consisting of two of the seven splice variants of FP was found to mediate ocular hypotension by prostamide-$F_{2\alpha}$ (27).

A great deal of effort has been dedicated to unravel the causes of adverse effects of the COX-2 inhibitors. One major reason is that activation of the IP receptor by PGI_2 is crucial for cardioprotection; reduced synthesis of this prostanoid by COX-2 inhibitors increases the risk for myocardial infarction, stroke and atherosclerosis (28, 29). In addition, there is an established link between impaired renal function and cardiovascular events such as myocardial infarction. Thus, the other possibility for the adverse effects of COX-2 drugs is the inhibition of constitutively expressed COX-2 in kidney with consequent disruption of renal function (18, 19). Studies suggest that COX-2 inhibition leads to altered expression of >1000 genes in renal medulla, including the genes that regulate synthesis of endogenous asymmetrical dimethyl arginine (ADMA), and monomethyl-L-arginine (L-MMA), compared to a smaller number of gene expression changes in heart or aorta. COX-2 deletion or inhibition increases the levels of ADMA and L-MMA, which in turn inhibits endothelial nitric oxide synthase (eNOS). eNOS is also cardioprotective, reducing thrombosis and atherosclerosis (30). It is not clear at this time whether the effect of COX-2 inhibitors on vascular IP receptors, or on the renal induction of nitric oxide synthase inhibitors (AMDA or L-NMMA), is the predominant cause of adverse effects. Nonetheless, both of these events could lead to severe cardiovascular adverse effects, suggesting that targeting COX-2 with small molecule inhibitors will be unfavorable for the treatment of peripheral or CNS chronic inflammatory diseases. These data suggest that identification and targeting of a specific prostanoid receptor down-stream of COX-2 is a good strategy for therapeutic development, both for inflammatory peripheral diseases and CNS diseases as discussed below.

3. Cyclooxygenases as therapeutic targets in seizure disorders

Numerous attempts have been made to alter the expression or activity of COX-2 to investigate its role in seizures. This intense investigation using *in vitro* and *in vivo* models of neuronal hyperexcitability and excitotoxicity has taken advantage of two key tools: mice that

lack COX-2 either globally or in a cell-specific manner, and COX-2 inhibitors (selective and non-selective). Conditional COX-2 knockout mice have proven useful as selective ablation of COX-2 in principal forebrain neurons (Figure 2) results in neuroprotection and a less robust inflammatory response following status epilepticus (SE) (31). Although manipulation of the COX-2 gene is very useful to investigate the role of COX-2 signaling in seizures, other studies examined the benefit of pharmacological inhibition of COX-2. The effects of COX-2 inhibitors on acute seizures have been explored in various acute rodent seizure and epilepsy models, with inconsistent outcomes (32). The timing of administration of the COX-2 inhibitor varies among the studies in Table 2 and appears important. For example, COX-2 inhibitors often have a beneficial outcome when administered within a few hours after a seizure (Table 2). Due to the differences in subject species, the convulsant, seizure duration and treatment paradigm, the efficacy of COX-2 inhibition to reduce acute seizure severity, intensity, and frequency has been inconsistent (Table 2).

The COX-2 inhibitor etoricoxib, when administered long-term to Wistar Albino Glaxo rats from Rijswijk (WAG/Rij, a recognized genetic animal model of absence epilepsy), reduced the development of spontaneous absence seizures (33). Similarly, daily intraperitoneal administration of etoricoxib at 1 mg/kg, but not at 10 mg/kg for eight days prior to PTZ kindling in rats had an anticonvulsant effect (34). On the other hand, the COX-2 inhibitor aceclofenac exhibited proconvulsant effects in a penicillin-induced experimental rat seizure model when administered intraperitoneally at two doses (10 and 20 mg/kg), 30 minutes after administering penicillin intracranially (35). More recently, a series of structurally novel COX-2 inhibitors were created (36). The lead compound in this series (MTL-1) displayed a significant anti-seizure effect in the PTZ kindling model when administered intraperitoneally at 30 mg/kg daily for 28 days (36). The efficacy of these novel COX-2 inhibitors as potential anticonvulsants is still under investigation in acute rodent epilepsy models.

Several clinical investigations have been made to explore potential beneficial outcomes for epilepsy of nonsteroidal anti-inflammatory drugs (NSAIDS) that inhibit COX-1 and COX-2. A large-scale observational study performed in Taiwan between 2000 and 2011 reported that long-term NSAID treatment reduced the incidence of epilepsy in patients suffering from rheumatoid arthritis (RA) (37). In this retrospective study, patients above the age of 20 diagnosed with RA or controls matched for age, gender and comorbidities were followed from the incidence date until the epilepsy diagnosis or the end of the study. People who developed RA had a higher risk of developing epilepsy, type unspecified (37). Interestingly, as shown in Fig 3 the incidence of epilepsy negatively correlated to the duration of treatment with NSAIDs in the RA population (37), suggesting that longer NSAID treatment could reduce the risk of epilepsy in this cohort. In this study all NSAIDS at any dose were lumped together. Additional clinical evidence of the ability of NSAIDs to control or modify seizures was suggested in patients suffering from Sturge-Weber syndrome (SWS), which is a congenital neurological disorder that often involves malformation of blood vessels in the pia mater and underlying cortex. A retrospective study followed nine patients with SWS (38). Six of the nine patients underwent long-term aspirin treatment and three patients used aspirin sporadically. The authors concluded that aspirin use correlated with clinical improvement (38). Another open label study on patients suffering from SWS investigated the efficacy of aspirin (3-5 mg/kg per day) in 58 patients aged 1 month to 144 months and

diagnosed with epilepsy. Aspirin use was associated with reduced seizure occurrence compared with historical controls (39). Ibuprofen was also investigated for its ability to alter seizures in 230 patients that had experienced febrile seizures. Children ages 1-4 who had experienced at least one febrile seizure and had a family history or other risk factor for subsequent febrile seizures were enrolled in a randomized, double blind, placebo-controlled trial. Upon the appearance of a fever, ibuprofen or placebo was administered at 5 mg per kilogram body weight every 6 hours until the patient was afebrile for 24 hours (40). Using the first seizure as the primary outcome, the authors found that ibuprofen had no beneficial effect on the rate of febrile seizure reoccurrence. Taken together, clinical investigations of the efficacy of NSAIDs to control or modify seizures suggest that long-term treatment could reduce the risk of developing epilepsy or result in lower seizure frequency in some epileptic patients. However, the potential benefits of long-term NSAID or coxib treatment must be weighed against their well-known adverse effects. By investing attention to the downstream effector molecules in the COX signaling cascade, such as the prostanoid receptors that offer more selective targets as discussed below, the complications of COX inhibition as an epilepsy disease modifying strategy might be overcome.

4. PGE_2 receptors

Three PGE synthase variants are known, one of which, PGES or mPGES-1, is inducible along with COX-2 and mediates inflammation-associated pain (41). COX-2 and all three PGE synthases are abundantly expressed by forebrain neurons and thus PGE_2 should be a prominent product of COX-2 in the forebrain. PGE_2 acts on four G-protein coupled receptors as shown in Figure 1. Although each of the EP receptors is somewhat promiscuous with respect to preferred G-protein, EP1 couples predominantly through Gαq to modify cellular Ca^{2+} signaling, whereas EP2 and EP4 couple canonically through Gαs and act to elevate cytoplasmic cAMP levels; several splice variants of EP3 exist, which are considered to couple mainly to Gαo or Gαi and blunt cAMP formation (42). Selective agonists and antagonists now exist for each of the prostanoid receptors (http://www.guidetopharmacology.org/GRAC/FamilyDisplayForward?familyId=58), which greatly facilitates exploration of their physiological and pathological roles in conjunction with the older generation of global knockout studies.

In an epilepsy context, most effort has been focused on EP1 and EP2. Systemic pharmacologic block of EP1 receptors 30 min before pentylenetetrazol (ip) delayed the onset of both myotonic and tonic-clonic seizures in Swiss mice, and reduced the total time spent in seizures (43). Likewise, global ablation of the EP1 gene in mice reduced their likelihood to enter status epilepticus after systemic kainic acid (44). Both findings suggest a role for EP1 in setting neuronal excitability. Following the demonstration that NSAIDs could prevent seizure-induced upregulation of p-glycoprotein, which can function to pump drugs out of the brain (45), the EP1 antagonist, SC-51089, was found to recapitulate this effect and to reinstate an anticonvulsant effect of the p-glycoprotein substrate, phenobarbital, in a kindling model (46). This suggests a potential disease-modifying opportunity for EP1 antagonists in pharmacoresistant epilepsies (47). Aside from the single report that intraventricular pretreatment of rats with an EP4 antagonist increases the latency for seizures

produced by pentylenetetrazol (48), nothing is known about the role for EP4 in seizure disorders.

Recognizing that EP2 activation plays extensive roles in peripheral inflammatory diseases (49–51), we developed novel EP2 antagonists to carry out proof of principal studies in rodent models of status epilepticus (SE) (22, 52–57). Administration of a brain-permeant competitive EP2 antagonist to mice or rats, beginning hours after onset of SE caused by pilocarpine or diisopropyl fluorophosphate (DFP), had several beneficial effects. Neuroinflammation in hippocampus was reduced as measured by microglial activation and induction of a panel of cytokines, neurodegeneration in hippocampus was blunted, and the typical opening of the blood-brain barrier that normally follows SE was abolished (54, 56). See Figure 4. In the DFP rat model, the gradual development of a memory deficit as assessed by novel object recognition was prevented by short-term post-SE treatment with an EP2 antagonist (57). Interestingly, all these effects recapitulated the effects of conditionally ablating COX-2 in principal forebrain neurons (31, 58), which suggests that most of the deleterious consequences of COX-2 induction by seizures are mediated by activation of EP2 receptors. It is important to note that the beneficial effects of the COX-2 conditional knockout, or of the EP2 antagonist, are not due to lessening of the intensity of SE itself as assessed by behavioral and EEG indices of seizures.

An interesting feature of EP2 antagonist therapy is that the drug must be administered with a delay of 2-4 hr after SE onset to be effective; for example administration 1 hr before or 1 hr after SE onset did not alleviate the weight loss that typically follows SE (55). Delayed treatment was also necessary in the rat DFP model (56). In both mouse pilocarpine and rat DFP models of SE, COX-2 was induced starting 2 hr after SE but not before (55, 56) suggesting that the therapeutic window of EP2 antagonists is determined by the time course of induction of COX-2 and the consequent increased production of PGE2. Paradoxically, intraventricular injection of the EP2 agonist, butaprost, immediately after SE termination is neuroprotective in rats (31), further suggesting that EP2 activation during or early after SE could be protective whereas delayed activation mediates pathology. It thus seems that EP2 has multiple roles after SE. Cell-specific conditional ablation of EP2 is underway to determine whether activation of EP2 on neurons is largely protective after SE whereas activation of EP2 on myeloid cells (monocytes and microglia) is primarily detrimental.

5. PGD_2 receptors

Prostaglandin D2 (PGD_2) participates in numerous biological functions, including inhibition of platelet aggregation (59), smooth muscle relaxation and contraction (60), vasodilation and vasoconstriction (61), and sleep induction (62). PGD_2 is the most abundant lipid metabolite derived from the release of arachidonic acid in rodent brains (63, 64), but it is unlikely to be formed in neurons. Two different synthases convert PGH_2 to PGD_2, termed hematopoietic (H-PGDS, encoded by the *HPGDS* gene) and lipocalin PGD_2 synthase (L-PGDS, encoded by the *PGDS* gene), also known as β-trace protein. In the brain the two PGD_2 synthases are largely expressed by different cell types, H-PGDS being found in microglia (65) and L-PGDS in leptomeninges, choroid plexus, and oligodendrocytes in adult rats and human (66, 67). L-PGDS is also secreted into serum, urine and seminal plasma. L-PGDS is the only

member of the lipocalin family that has the dual function of converting PGH_2 to PGD_2 and also binding to and transporting small lipophilic molecules such as retinoids, bilirubin and biliverdin, GM1 and GM2 gangliosides and amyloid beta. L-PGDS is upregulated in the brain of various animal models of neurodegenerative diseases such as the demyelinating twitcher mouse (68), and mouse models of lysosomal storage diseases including Tay-Sachs' and Sandhof's diseases, GM1 gangliosidosis and Niemann-Pick disease (69).

To execute its physiological activities, PGD_2 binds two receptors, DP1 and DP2 (CRTH2). DP1 receptors are expressed by cells in the leptomeninges on the ventral surface of the rostral basal forebrain of mice, whereas other brain areas are almost completely devoid of these receptors (62). Both DP receptors are G protein coupled receptors; DP1 is Gαs-coupled while DP2 is Gαi coupled. PGD_2-DP1 signaling is known to regulate selected central nervous system functions, typically pain sensation, food intake and sleep-wakefulness cycle (62, 70, 71). DP2 is expressed on immune Th2 cells, eosinophils and basophils and mediates the chemotaxis of those cells toward PGD_2 (72). A recent study indicated that activation of DP2 in central nervous system can cause signs interpreted as emotional liability in mice. LPS-induced sickness behavior, social impairment as well as induction of c-Fos expression in the hypothalamic paraventricular nucleus and central amygdala were dependent on the presence of DP2 and those effects could be reversed by the selective DP2 antagonist, CAY10471, delivered intracerebroventricularly (73).

Under basal conditions, PGD2 level is relatively low in the brain but is remarkably elevated during seizures induced by pentylenetetrazol (74). A role for DP1 activation in pentylentetrazol (PTZ) induced seizures is supported by the finding that genetic ablation of H-PGDS and DP1, but not L-PGDS or DP2, decreased the incidence and increased the intensity of seizures (75). Moreover, the L-PGDS/PGD_2/DP1 system appears to modulate postictal sleep after seizures (75). It will be important to follow up these observations with other seizure models and cell-specific conditional ablation of PGD_2 receptors to better understand the role of the DP1 and DP2 receptors in seizure disorders.

6. $PGF_{2\alpha}$ receptors

The $PGF_{2\alpha}$ receptor (FP) is activated by the prostanoid $PGF_{2\alpha}$, which is derived from PGE_2, PGD_2, or PGH_2 by PGE 9-ketoreductase (*cbr1*, encoding carbonyl reductase), PGD 11-ketoreductase (*akr1c3*), or PGH 9-, 11- endoperoxide reductase, respectively (76). CBR1 is expressed at high levels by hippocampal pyramidal cells and cortical neurons (Allen Brain Atlas), making it likely that much of the $PGF_{2\alpha}$ measured in the brain actually derives from PGE_2. $PGF_{2\alpha}$ has been demonstrated in CA3 pyramidal cells of the hippocampus after seizures (77). On the other hand, AKR1C3 appears to be a major source of $PGF_{2\alpha}$ in peripheral tissues. FP is encoded by the *PTGFR* gene, containing 7 exons and expressed as two alternatively spliced transcript variants. Gene expression analysis in mouse brain cells isolated from naïve mice reveals low expression in brain tissue with detectable levels of *Ptgfr* mRNA in astrocytes and neurons (78). Outside of the CNS, FP is highly expressed in uterine smooth muscle and, interestingly, female FP knockout mice cannot perform parturition due to the absence of labor (79), highlighting an important role for FP signaling in reproduction. Together with prostanoid receptors EP1 and TP, FP is classified as a

"contractile" prostaglandin receptor because activation of these receptors induces smooth muscle contraction through cytoISI:000187888700027solic Ca^{2+} mobilization (80). Protein kinase C (PKC) and Ca^{2+} mobilization are initiated through FP coupling to Gαq and subsequent activation of phospholipase C (PLC). There is also evidence suggesting that FP can couple to Gα12/13 to activate Rho (81).

Insights into the roles of FP signaling in the brain have largely been inferred from FP knockout mice in stroke models. FP knockout mice display smaller infarct volume and attenuated excitotoxic brain damage in the unilateral middle cerebral artery occlusion (MCA) model of focal cerebral ischemia when compared to FP-sufficient controls. Notably, a FP agonist exacerbated infarct size in FP-sufficient animals, but not in FP knockout mice (82). Moreover, administration of a FP antagonist after permanent middle cerebral artery occlusion resulted in attenuated deficits in behavior and smaller infarct size (83). Administration of the FP partial antagonist, AL-8810, was also protective in a traumatic brain injury mouse model, resulting in reduced hippocampal swelling, improved behavior, and reduced microgliosis 10 days after TBI (84). Taken together these findings indicate that FP activation is deleterious in at least three different brain injury models.

Elevated cerebral spinal fluid levels of $PGF_{2\alpha}$ have been reported in children who experienced a febrile seizure or meningitis, but not in epileptic children (85). $PGF_{2\alpha}$ levels are relatively low in multiple brain regions in convulsion-prone gerbils. However, after environment-induced convulsions in gerbils, $PGF_{2\alpha}$ levels elevate over five-fold within three minutes in cortex and hippocampus (86). $PGF_{2\alpha}$ levels begin to elevate in rat brain within 10 minutes after subcutaneous injection of kainic acid (87), presumably being converted from PGE_2 or perhaps PGD_2. Histological examination of rat brain tissue 30 minutes after kainic acid-induced seizures reveals $PGF_{2\alpha}$ immunoreactivity in CA3 hippocampal neurons, hilar neurons, and granule cells of the dentate gyrus, suggesting these hippocampal neuronal populations are the major brain source of $PGF_{2\alpha}$ after kainic acid-induced seizures (77), again, likely via isomerization of PGE_2. Moreover, hippocampal $PGF_{2\alpha}$-immunoreactive neurons also express PLA_2, Cox-2, and FP receptor. Taken together these findings demonstrate that $PGF_{2\alpha}$ is rapidly synthesized in response to seizure activity and may mediate a role in the acute phases of seizure activity.

Hypoxia-induced neuronal cell death in rat cortical primary cultures is exacerbated when $PGF_{2\alpha}$ is applied to the culture medium prior to anoxic exposure (88), suggesting FP activation has deleterious consequences on neuronal survival. In contrast, intracisternal application of $PGF_{2\alpha}$ suppressed kainic acid-induced seizures and prevented neuronal cell loss in the mouse hippocampus (89). In the same study, FP receptor antagonism potentiated kainic acid-induced seizures, suggesting that FP activation via $PGF_{2\alpha}$ can be anti-convulsant and neuroprotective. In contrast to the aforementioned studies, intra-amygdala administration of massive doses of $PGF_{2\alpha}$ had no effect on seizure activity in kindled rats (90). Taken together these studies reveal that the consequences of FP activation on seizure activity remain poorly understood. The reasons for these discordant experimental findings remain unclear. It is likely that the effects of FP activation on neuronal survival and seizure intensity are context-dependent.

7. Three therapeutic goals in epilepsy.

The first goal is to suppress seizures in people with epilepsy, accomplished with anticonvulsants that elevate seizure threshold. They must be taken chronically. Seizures are uncontrolled in approximately one third of epilepsy patients (i.e., in 1.3-1.5 million people in the U.S.), a group who could benefit from novel anticonvulsants. The second goal is discovery of epilepsy prevention drugs that would be administered for a short period of time to people at risk for developing epilepsy, and result in the epilepsy risk subsiding to that of the general age-matched population. With a lifetime risk of ~3.8% (94), up to 15 million adults in the U.S. could benefit from an epilepsy prevention drug. The third goal is disease modification that would occur if, following brief administration of a drug to an at-risk patient: the onset of epilepsy is delayed; upon developing epilepsy, the frequency or intensity of spontaneous seizures is reduced (i.e., partial or complete remission); comorbidities such as anxiety, depression, or cognitive deficits are prevented; or pharmacoresistant epilepsy is converted to drug-manageable epilepsy.

8. Conclusions

The cyclooxygenases, particularly COX-2, sit in the middle of major inflammatory lipid signaling cascades that are engaged by most environmental risk factors for developing epilepsy, namely head trauma, parasitic infections such as neurocysticercosis, tumors and de novo status epilepticus. The animal literature is inconsistent regarding the potential benefits of pan-specific NSAIDS or COX-2 selective coxibs in epilepsy models, as expected when interfering with a multi-dimensional signaling pathway.

There is limited clinical experience with NSAIDS in epilepsy prevention, although one large scale observational study reported that Taiwanese adults who developed rheumatoid arthritis had increased risk of epilepsy, and that long-term use of NSAIDS reduced this risk. Small scale open-label studies of the treatment of Sturge-Weber syndrome patients with NSAIDs were also favorable. Taken together, the clinical data are encouraging of further, prospective, studies. Following the aforementioned risk events in animal models, COX-2 is rapidly induced in principal glutamatergic neurons of the hippocampus, cortex and associated areas such as the lateral amygdala nucleus. All three PGE synthases are abundantly expressed by these forebrain neurons, together with an enzyme that converts PGE_2 to $PGF_{2\alpha}$, and thus PGE_2 and $PGF_{2\alpha}$ should be prominent products of COX-2 in the forebrain. A proconvulsant effect of EP1 activation has been inferred from the effects of an EP1 antagonist or global ablation of the EP1 gene in rodent seizure models, which perhaps explains the observations of an anticonvulsant effect of NSAIDs. Delayed EP2 activation, however, appears to be largely responsible for the neuroinflammation, neurodegeneration and BBB breakdown that is caused by COX-2 induction. Taken together the preclinical and clinical studies are consistent with roles for downstream cyclooxygenase signaling in the processes underlying the development of epilepsy and associated neuroinflammation. However, coxibs are expected to enhance leukotriene and endocannabinoid signaling as well as suppress prostanoid actions, which complicates mechanistic interpretation of the biological effects of these agents.

9. Expert opinion

Anticonvulsant targets are few – approximately 35 FDA-approved drugs target sodium, potassium and T-type calcium channels, $GABA_A$ receptors, GABA transaminase, SV2A synaptic vesicle proteins and cannabinoid receptors. These drugs all act to suppress seizures in people with epilepsy yet are insufficiently effective in one third of patients. An intense effort is underway to discover strategies for epilepsy prevention or disease modification, which currently don't exist. This effort, and the drive to develop new anticonvulsants, are expected to require exploration of new processes, pathways and proteins with the goal of elevating the seizure threshold while having acceptable side effects (91). Processes that can influence seizure thresholds include neuronal and glial plasticity, patchy breakdown of the blood brain barrier, and neuroinflammation. Given the major role that COX-2 signaling pathways serve in peripheral inflammatory diseases such as rheumatoid arthritis and inflammatory bowel disease, therapeutic opportunities for inhibitors of cyclooxygenases and downstream prostanoid receptors in epilepsy remain promising, but unfulfilled.

Why hasn't the cyclooxygenase signaling cascade been pursued more vigorously for epilepsy in a clinical setting? We suspect there might be three issues. First, conversations with pharmaceutical executives reveal a strong worry about serious adverse events similar to those caused by COX-2 inhibitors such as Vioxx. These concerns are not fully assuaged by knowledge of the toxicity mechanism for coxibs even when a likely strategy to avoid these toxicities is to select specific targets downstream of the COX-2 enzyme. Second, the state of knowledge about the neurobiological effects of other major neuroinflammatory mediators – IL-1β, TNF-α and TGF-β– is currently deeper than that of the prostanoids and especially prostamides, which could reduce the comfort level with these new targets. One concern is that eicosanoid signaling might be so interwoven into activities of daily living that drug development proves intractable. Third, cyclooxygenase inhibition should also cause accumulation of endocannabinoids and has the theoretical downside of shuttling arachidonic acid to the lipoxygenase pathway hence to leukotriene and lipoxin production (Figure 1), further complicating a mechanistic understanding of clinical benefits. Monoacylglycerol lipase (MAGL) inhibitors, which limit arachidonic acid levels, might be a better alternative to NSAIDs or coxibs. MAGL is a large source of arachidonic acid and thus eicosanoids in brain (92), and is highly expressed in hippocampal and cortical neurons according to the Allen Brain Atlas. Its inhibition suppresses ongoing status epilepticus (93). However, whether this is due to build-up of endocannabinoid lipids or their metabolites, reduced prostaglandin or leukotriene production, or a combination, is unknown. On the positive side, several retrospective or observational clinical studies point to potential clinical benefits of NSAID treatment in epilepsy. Whether COX-1 or COX-2 is the primary NSAID target is not known from the data, and prospective clinical studies with selective drugs are greatly needed.

Downstream prostanoid synthases or receptors present drug targets that should offer a more limited palette of adverse effects than COX-2 inhibition itself. EP2 and potentially EP1 appear especially promising at this point. An EP1 antagonist could find use in pharmacoresistant epilepsies that are caused by induction of the p-glycoprotein drug pump, although it would be worthwhile to replicate the original findings (46) with a more selective

EP1 antagonist (e.g., ONO-8713). EP2 antagonists have now been found to provide neuroprotection, to dampen the inflammatory reaction, and to preserve the integrity of the blood brain barrier in two animal models of status epilepticus without affecting the intensity of status epilepticus itself. Moreover, in the DFP rat model, short-term treatment with an EP2 antagonist prevented the development of a novel object recognition deficit two months later (57), suggesting a potential adjunctive use for cognition-related consequences of seizures. The EP2 therapeutic window opens several hours after status epilepticus, coincident with the time of COX-2 induction. This both complicates clinical application and presents an opportunity for adjunctive use with benzodiazepines and anticonvulsants in treatment of refractory SE.

Taken together, these observations highlight the complexity of inflammatory lipid signaling in the brain. A picture is emerging whereby neuronal release of PGE_2 from constitutively expressed COX-2 during SE activates EP2 on nearby neurons to promote neuroprotection and blood-brain barrier integrity, then a few hours later neuronal COX-2 is induced, causing massive PGE_2 release that activates EP2 on nearby microglia to trigger an inflammatory reaction with accompanying neuronal injury and exacerbation of blood-brain barrier breakdown. A major question is whether timely application of an EP2 antagonist will prevent, delay or modify the development of epilepsy in animals at risk, for example after status epilepticus or head injury. Regardless of the outcome of these experiments, delayed administration of an EP2 antagonist would appear to be a viable adjunctive treatment to attenuate the pathology attendant status epilepticus.

Numerous unresolved issues and uncertainties are pertinent for the optimum selection of drug targets for epilepsy and epileptogenesis among the various synthases and receptors that comprise the extensive lipid signaling cascade represented in Figure 1. Among the most interesting and potentially useful questions are the following: What are the mechanisms and biochemical pathways underlying prostanoid-driven neuroinflammation? Does the anti-inflammatory effect (and clinical value) of coxibs rely predominantly on reduced prostanoid production or on elevated levels of leukotrienes, lipoxins and endocannabinoids? What receptors are activated by the COX-2 derived prostamides and prostaglandin glycerol esters, and how does their biology differ from that of the prostaglandins themselves? What cell types mediate the inflammatory effects of EP2 activation after seizures? For the last question, our current efforts use cell-specific conditional ablation of the EP2 gene in comparison with systemic EP2 antagonism in epilepsy models.

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Article Highlights

1. COX-2 promotes inflammation via the synthesis of prostaglandins and endocannabinoid metabolites.
2. Long-term treatment with NSAIDs might reduce the risk of developing epilepsy.
3. Receptors for PGE_2, and potentially PGD_2, and $PGF_{2\alpha}$, are potential therapeutic targets for epilepsy.
4. Selective EP2 receptor antagonism following status epilepticus produces a number of beneficial effects.
5. Activation of EP1 and FP exacerbates seizures via intracellular Ca^{2+} mobilization pathways.
6. Brain PGD_2 and $PGF_{2\alpha}$ levels are remarkably elevated during seizures, the latter likely secondary to massive synthesis of PGE2.

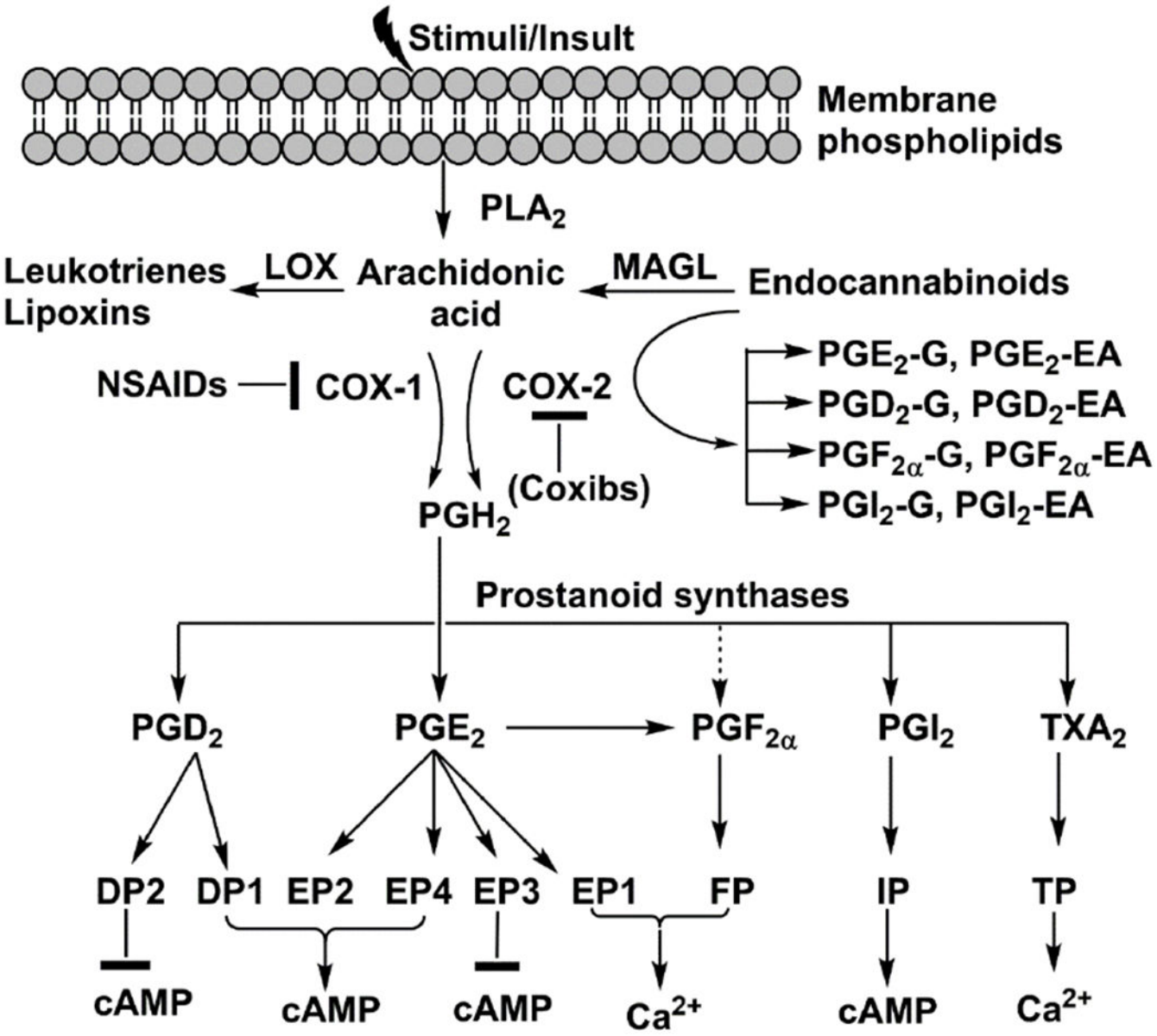

Figure 1. Cyclooxygenase signaling cascades

Both Cyclooxygenase 1 (COX-1) and Cyclooxygenase 2 (COX-2) enzymes convert arachidonic acid to prostaglandin H2 (PGH_2). Cell specific syntheses convert PGH_2 intermediate into prostaglandin ligands, which activate one or more G protein-coupled prostanoid receptors. Much of the prostaglandin F2α ($PGF_{2\alpha}$) in the brain is derived from reduction of prostaglandin E2 (PGE_2). COX-2 also metabolizes endocannabinoids to prostaglandin analogs (glycerol esters and ethanolamides), which likely activate receptors distinct from those of the prostaglandins. Four receptors, prostaglandin D2 receptor 1 (DP1), prostaglandin E2 receptor 2 (EP2), prostaglandin E2 receptor 4 (EP4) and prostacyclin receptor (IP), promote cyclic adenosine monophosphate (cAMP) production. cAMP activates (protein kinase A) PKA and or exchange protein directly activated by cAMP

(Epac) signaling. COX-1 and COX-2 inhibition would block the entire prostanoid receptor activity, and thus may lead to adverse-effects.

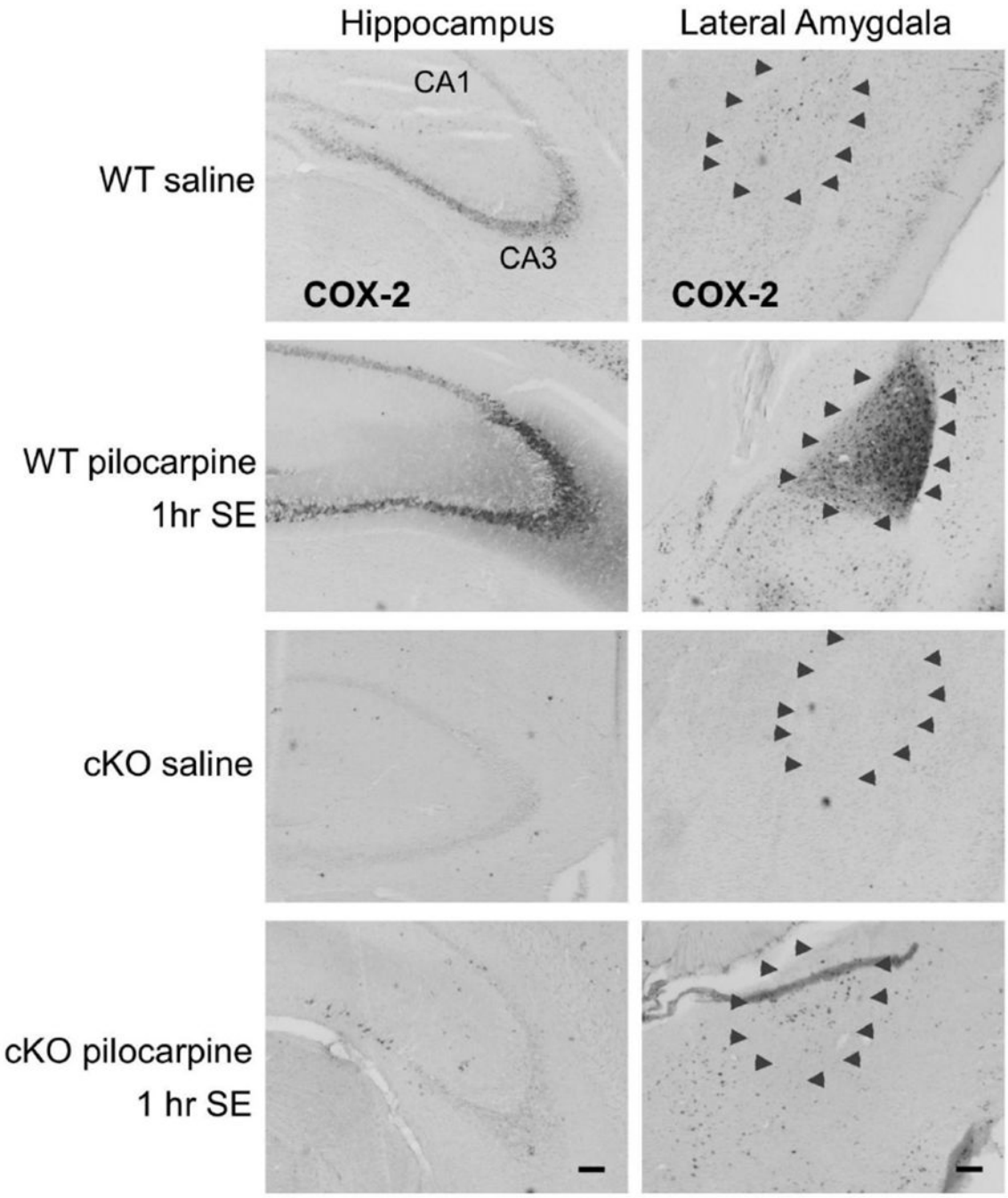

Figure 2. Conditional ablation of COX-2 in forebrain neurons

Coronal sections (30 μm) were incubated with the COX-2 antibody (Abcam, 1:1000) and subsequently with a biotin conjugated goat anti-rabbit secondary antibody. The sections were incubated with HRP-conjugated streptavidin and developed with diaminobenzidine (DAB). Immunostaining for COX-2 demonstrates expression in the pyramidal cell layers of the hippocampus and lateral amygdala in wildtype mice, but not in the conditional knockout (cKO) mice. One day after 1 hour of status epilepticus (SE) induced with pilocarpine (280

mg/kg), COX-2 induction is observed in wildtype forebrain neurons, but not in cKO forebrain neurons. Scale bar, 100 μm. The arrowheads outline the lateral amygdala.

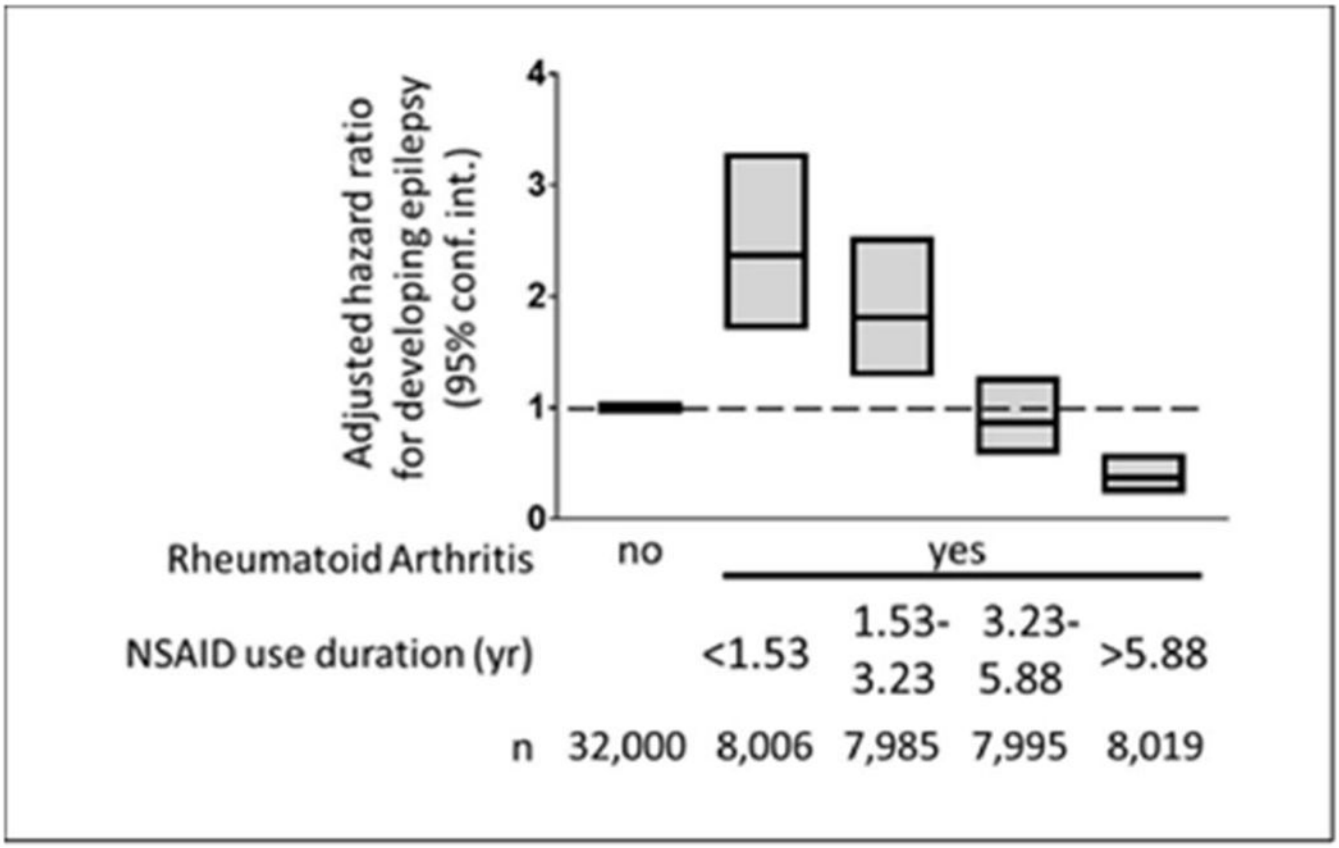

Figure 3. Evidence consistent with a disease-modifying effect of chronic NSAID use in epilepsy

32,007 adults with rheumatoid arthritis (RA) but without a pre-existing epilepsy diagnosis were selected from the National Health Insurance research database of Taiwan and were matched for gender and age with a similar number of controls. International classification of diseases (ICD-9-CM) codes were used to define diseases. The RA cohort was separated into quartiles based on the length of time nonsteroidal anti-inflammatory drugs (NSAIDs) were taken. The cumulative incidence of epilepsy was assessed in each group using a Kaplan-Meier method. Data from Table 4 of reference (37) are plotted as median and 95% confidence intervals of the adjusted hazard ratio for developing epilepsy. These results suggest that rheumatoid arthritis might increase risk of developing epilepsy, and that the risk is mitigated by chronic NSAID use.

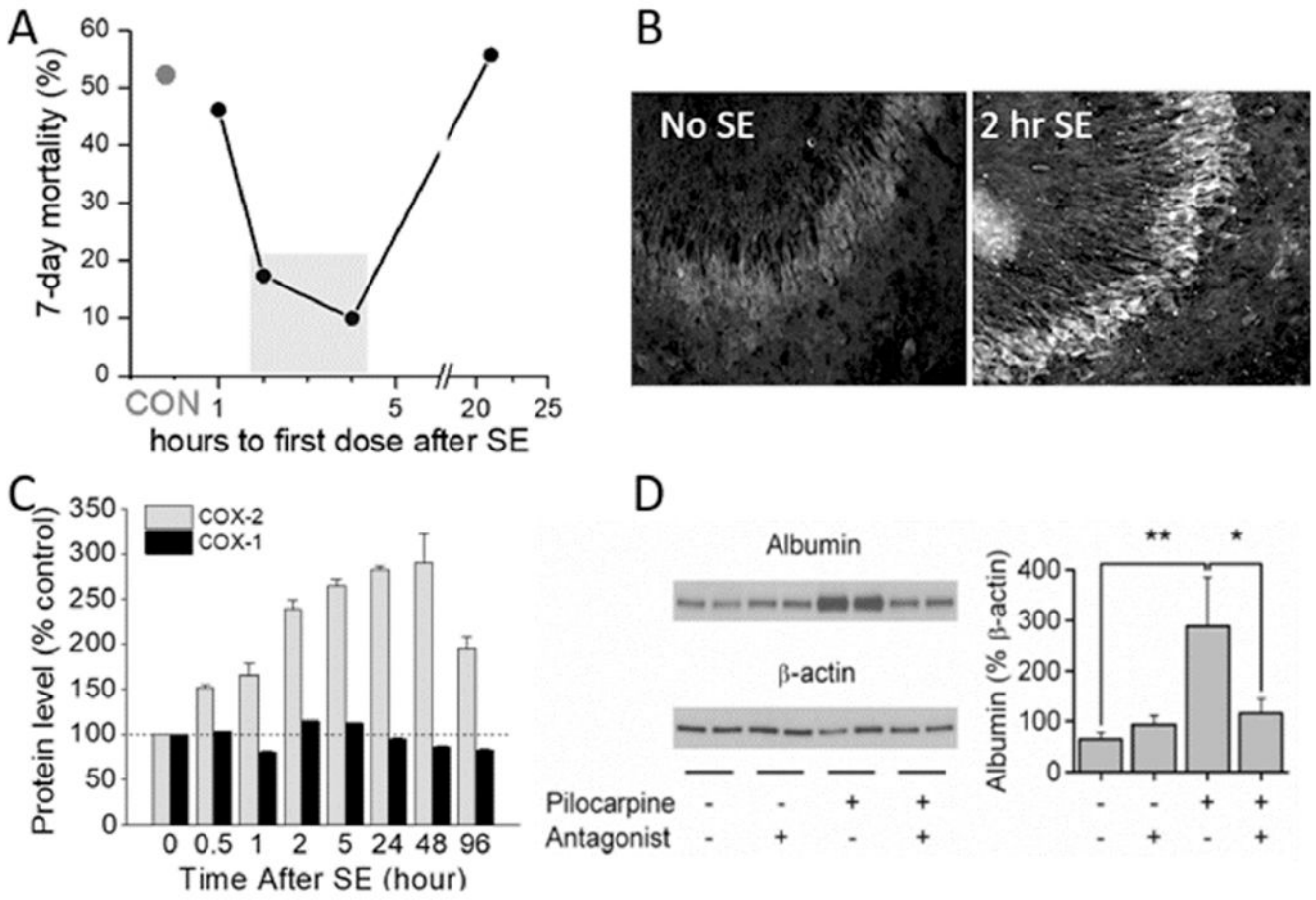

Figure 4. Therapeutic window of EP2 antagonist matches COX-2 induction time course

A. Delayed mortality mice that had experienced 1 hour of pilocarpine-induced status epilepticus (SE) and survived at least 12 hours. A brain-permeant prostaglandin E2 receptor 2 (EP2) antagonist (TG6-10-1) was administered in divided doses beginning at the times on the x-axis. ***B***. Induction of cyclooxygenase 2 (COX-2) immunoreactivity in cornu ammonis 3 (CA3) pyramidal cells as early as 2 hours following SE induced in rats by diisopropyl fluorophosphate (DFP). ***C***. Measurement of COX-1 and COX-2 protein levels in hippocampus at different times after DFP-induced SE onset. ***D***. EP2 receptor antagonist maintains the integrity of the blood–brain barrier after SE. Serum albumin leak into the cortex 4 d after pilocarpine-induced SE was used to assess the integrity of the blood–brain barrier. The EP2 antagonist, TG6-10-1, was administered in three doses between 4 and 30 hours after SE onset. The albumin protein levels in cortices of control or SE mice that received vehicle or TG6-10-1 were measured by Western blot with β-actin as loading control. The normalized band intensity of the albumin protein is shown (n = 3-6, $*p < 0.05$, $**p < 0.01$, one-way ANOVA and post hoc Bonferroni test with selected pairs). A from ref. (55); B and C from ref. (56); D from ref. (54).

A is reproduced from Jiang J, Yang MS, Quan Y, et al. Therapeutic window for cyclooxygenase-2 related anti-inflammatory therapy after status epilepticus. Neurobiol Dis. 2015;76:126-36. Epub 2015/01/21. doi: 10.1016/j.nbd.2014.12.032 with kind permission from Elsevier.

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Table 1.

Major innate immune pathways of sterile inflammation in the brain

Initiator	Mediators	Effector pathways	Cellular consequences
↑ Neuronal [Ca2+]	COX-2 → **PGE2** → EP2, EP1	PKA, Epac, β-arrestin, PKC	Cytokine regulation, vascular control
HMGB1	TLR4 → **IL-1β** → IL-1R	MyD88, IRAC1, NF-kB	↓ K_{Ca}, ↑NMDAR, ↓GABA-AR
HMGB1, cytokines	**TNF-α** → TRADD, TRAF2	ASK1, PI3K, AKT, caspase 3, NF-kB, AP-1	Cell death, Transcriptional regulation (esp. IL-1, IL-6, COX-2)
MMP9, plasmin, thrombospondin	**TGF-β, (albumin)** → TGFBR1, TGFBR2	Smad2/3, p38-JNK, PI3K/AKT, Rho/Rac	Transcriptional regulation ↓ Kir4.1 on astrocytes
Not known	**CCL2** → CCR2	PI3K, PKC	Monocyte recruitment

HMGB1, high mobility group box 1; MMP9, matrix metallopeptidase 9; COX-2, cyclooxygenase 2; PGE2, prostaglandin E2; EP1, prostaglandin E2 receptor 1; EP2, prostglandin E2 receptor 2; TLR4, toll-like receptor 4; IL-1b, interleukin 1 beta, Il-1R, interleukin 1 receptor; TNF-a, tumor necrosis factor alpha; TRADD, tumor necrosis factor receptor type 1-associated death domain protein; TRAF2, tumor necrosis factor receptor associated factor 2; TGF-b, transforming growth factor beta; TGFBR1, transforming growth factor beta receptor 1; TGFBR2, transforming growth factor beta receptor 2; CCL2, chemokine C-C motif ligand 2; CCR2, C-C chemokine receptor type 2; PKA, protein kinase A; Epac, exchange protein activated by cAMP; PKC, protein kinase C; MyD88, myeloid differentiation primary response 88; IRAC1, ixodes ricinus anti-complement protein 1; NF-kB, nuclear factor kappa light chain enhancer of activated B cells; ASK1, apoptosis signal regulating kinase 1; PI3K, phosphoinositide 3-kinase; AKT, RAC-alpha serine/threonine kinase; AP-1, activator protein 1; Smad2/3, mothers against decapentaplegic homolog 1 and homolog 2; p38, mitogen activated protein kinase; JNK, c-Jun N-terminal kinase; Rho, Ras homolog gene; Rac, Ras related C3 botulinum toxin substrate 1; Kca, calcium activated potassium channel; NMDAR, N-methyl-D-aspartate receptor; GABA-AR, gamma-aminobutyric acid A receptor; IL-1, interleukin 1; IL-6, interleukin 6; KIr4.1, inward rectifying potassium channel 4.1

Table 2.

Effects of COX-2 inhibitors on neuropathologies in rodent models of epilepsy.

COX-2 inhibitor	Convulsant	Seizure duration	Species, strain and gender	Dose of COX-2 inhibitor	Treatment paradigm of COX-2 inhibitor	Outcome of COX-2 treatment	Ref
Celecoxib	Kainate (12 or 6 mg/kg, ip.)	NT	Male Wistar rat	6 mg/kg, ip., once daily for 5 days or single injection	Given 2 hours after kainate injection	+	(95)
Celecoxib	Kainate (12 or 6 mg/kg, ip.)	NT	Male Wistar rat	6 mg/kg, ip., once daily for 5 days or single injection	Given 2 hours before kainate injection	−	(95)
Celecoxib	Pilocarpine (30 mg/kg, ip.)	60 minutes	Male Sprague-Dawley rat	20 mg/kg, p.o., once daily for 14 days	Given 24 hours after SE	+	(96)
Celecoxib	Pentylenetetrazol (60 mg/kg, ip.)	NT	Male Wistar rat	2 mg/kg, p.o., once	Given 1 hour before PTZ injection	+	(97)
Celecoxib	Pentylenetetrazol (60 mg/kg, ip.)	NT	Male Wistar rat	0.2 or 20 mg/kg, p.o., once	Given 1 hour before PTZ injection	−	(97)
Rofecoxib	Kainate (10 mg/kg, ip.)	NT	Male Sprague-Dawley rat	10 mg/kg, ip., twice daily for 3 days	Given 6 or 8 hours after KA injection	+	(98)
Rofecoxib	Pentylenetetrazol (ivt)	NT	Male Albino mice	4 mg/kg, ip., single injection	45 minutes before PTZ injection	+	(99)
Parecoxib (valdecoxib)	Pilocarpine (20-50 mg/kg, ip.)	90 minutes	Female Sprague-Dawley rat	10 mg/kg, ip., twice daily for 17 days	Given 90 minutes after SE onset	+/−	(100)
SC58125	Kainate (10 mg/kg, s.c.)	NT	Male Sprague-Dawley rat	3 mg/kg, p.o., once	Given 1 hour before KA injection	+	(101)
SC58125	Kainate (0.6 μg, ivt)	NT	Male Sprague-Dawley rat	3 mg/kg, p.o., 3 times	Given 1 hour before, 24 and 48 hours after the KA injection	+	(101)
NS398	Kainate (1 μg, intrahippocampal injection)	NT	Male Wistar rat	10 mg/kg, ip., twice daily for 3 days	Given 5 hours after KA injection	+	(102)

COX-2 inhibitor	Convulsant	Seizure duration	Species, strain and gender	Dose of COX-2 inhibitor	Treatment paradigm of COX-2 inhibitor	Outcome of COX-2 treatment	Ref
NS398	Kainate (1 μg, intrahippocampal injection)	NT	Male Wistar rat	5 mg/kg, ip., once	Given 30 minutes before KA injection	+	(102)
Nimesulide	Electrical stimulation of hippocampus	NT	C57BL/6J mice	10 mg/kg, p.o., single injection	Given 30 min Given before SE-induction	+	(103)
SC58236	Electrical stimulation of hippocampus	9-10 hours	Male Sprague-Dawley rat	10 mg/kg, p.o., once daily for 7 days	Given 4 hours after SE	+/−	(104)
SC58236	Electrical stimulation of hippocampus	9-11 hours	Male Sprague-Dawley rat	10 mg/kg, p.o., once daily for 3 days or for 14 days	Given 1 day before SE-induction	−	(105)
Etoricoxib	Genetically prone absence seizures	SRS	WAG/Rij rat	10 mg/kg/ day, for 17 weeks	Given every day for 17 weeks	+	(33)
Etoricoxib	Pentylenetetrazol (30 mg/kg, ip.)	NT	Male Wistar rat	1 mg/kg and 10 mg/kg, ip. once daily	Given every day for 9 consecutive days	+/−	(34)
Aceclofenac	Penicillin G potassium (500 units, i.c.)	4-5 hours	Male Wistar rat	10 mg/kg and 20 mg/kg, ip., once	Given 30 minutes after penicillin injection	−	(35)
MTL-1	Pentylenetetrazol (85 mg/kg, s.c.)	NT	Swiss albino mice	30, 100, 300 mg/kg, ip., once	Given 30 minutes or 4 hours after PTZ injection	+	(36)

The outcome measures were neuronal loss (neurodegeneration), acute seizures, recurrent spontaneous seizures, behavioral alterations, cognitive deficits, or combinations of these. A study was assigned a "+" if there was a beneficial outcome following treatment with a COX-2 inhibitor; "−" if there was no beneficial effect with the COX-2 inhibitor; "+/−" if there was a beneficial outcome for one measure and no effect on another. KA, kainate; NT, no termination; ip., intraperitoneal; ivt, intraventricular; sc., subcutaneous; p.o., per os; SE, status epilepticus; PTZ, pentylenetetrazol; SRS, spontaneous recurrent seizures