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Targeting cyclooxygenases-1 and -2 in neuroinflammation: therapeutic implications

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Abstract

Neuroinflammation has been implicated in the pathogenesis or the progression of a variety of acute and chronic neurological and neurodegenerative disorders, including Alzheimer's disease. Prostaglandin H synthases or cyclooxygenases (COX-1 and COX-2) play a central role in the inflammatory cascade by converting arachidonic acid into bioactive prostanoids. In this review, we highlighted recent experimental data that challenge the classical view that the inducible isoform COX-2 is the most appropriate target to treat neuroinflammation. First, we discussed data showing that COX-2 activity is linked to anti-inflammatory and neuroprotective actions and is involved in the generation of novel lipid mediators with pro-resolution properties. Then, we reviewed recent data demonstrating that COX-1, classically viewed as the homeostatic isoform, is actively involved in brain injury induced by pro-inflammatory stimuli including A β , lipopolysaccharide, IL-1 β , and TNF- α . Overall, we suggest revisiting the traditional views on the roles of each COX during neuroinflammation and we propose COX-1 inhibition as a viable therapeutic approach to treat CNS diseases with a marked inflammatory component.

Cyclooxygenases -1 and -2 in the central nervous system

Prostaglandin H synthases, or cyclooxygenases (COX), exist in two isoforms COX-1 and COX-2, encoded by different genes. A third isoform (COX-3 or COX-1b) has been first described in canine as a splice variant of COX-1 gene but its physiological role at this point remains unknown. Indeed, in rodents and humans, COX-1b encodes proteins with completely different amino acid sequences than COX-1 or COX-2 and without COX activity [1]. COX play a central role in the inflammatory cascade by converting arachidonic acid (AA), released from membrane phospholipids by a phospholipase A₂ (PLA₂), into bioactive prostanoids. Both COX isoforms catalyze the same reactions: dioxygenation of arachidonic acid (AA) to yield prostaglandin G₂ (PGG₂), and a peroxidase reaction, which converts PGG₂ to prostaglandin H₂ (PGH₂). PGH₂ is then transformed into PGE₂, PGF_{2 α} , PGD₂, PGI₂ and TXB₂ through specific terminal synthases (Fig. 1). The eicosanoids synthesized by COX are powerful lipid mediators that exert a variety of biological effects by acting on multiple G coupled protein receptors. The two COX isoforms share 60% homology in their amino acids sequence and are both integral membrane homodimers proteins of the endoplasmic reticulum and nucleus, with roughly comparable kinetics. However, they differ in their regulatory mechanisms, cell localization, and function. COX-2 was first identified as a key element of the acute inflammatory response because its expression is rapidly induced

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by various inflammogens [2]. Indeed, COX-2 gene has several transcriptional regulatory elements, including NF- κ B, Sp1, a TATA box, CAAT Enhancer Binding Protein Beta (C/EBP β), and cAMP response element-binding (CREB) consensus sequences, interacting with trans-acting factors generated by multiple signaling pathways [3,4]. In contrast, COX-1 promoter lacks a TATA or CAAT box, has a high GC content, and contains several SP1 elements. Moreover, COX-2, but not COX-1, contains a unique 27 amino acid sequence near its C-terminus, an instability element involved in COX-2 protein degradation [4]. Because COX-2 is typically induced by inflammatory stimuli in the majority of tissues, it was presumed to be the only isoform responsible for propagating the inflammatory response and thus traditionally considered as the best target for anti-inflammatory drugs. COX-2 selective inhibition, however, has been associated with an increased risk of severe cardiovascular adverse events, which led to the voluntary withdrawal from the market of some COX-2 selective inhibitors [5]. In the brain, both COX-1 and COX-2 are constitutively expressed. In physiological conditions, COX-1 is mainly expressed in microglia and perivascular cells (a macrophage-derived vascular cell type) [6–8] and COX-2 is found in post synaptic dendrites and excitatory terminals, particularly in the cortex, hippocampus and amygdala, with both neuronal and vascular associations [9]. Thus, it is not surprising that in the central nervous system (CNS) COX-2 has been implicated in important physiological functions such as synaptic activity, long-term potentiation, long-term depression, memory consolidation, and neurovascular coupling during functional hyperemia [10,11]. Furthermore, COX-2, but not COX-1, can oxygenate endocannabinoids, which represent an important metabolic pathway in neurons to regulate excitatory synaptic transmission [12]. Even in physiological conditions, COX-1 or COX-2-derived prostanoids seem to have distinct functions. For instance, PGE₂ resulting from COX-2, but not COX-1 activity, is necessary for the induction of long-term potentiation and spatial learning *in vivo*, whereas COX-1 inhibition facilitates baseline synaptic transmission [13].

Recent data have challenged the classical view describing COX-1 as the isoform merely responsible for physiological production of prostanoids and COX-2 as the major pro-inflammatory isoform. The use of genetic mouse models in combination with selective pharmacological inhibitors helped to identify the specific roles of COX-1 and COX-2 during neuroinflammation [14].

COX-2 activity is necessary to switch off neuroinflammation

Several studies have now demonstrated that COX-2 genetic deletion or pharmacological inhibition can worsen the response to neuroinflammatory stimuli. Specifically, Gilroy and collaborators provided the first evidence of COX-2 anti-inflammatory properties in a carrageenan-induced pleurisy model [15]. In the brain, our and other groups demonstrated that inhibition or genetic deletion of COX-2 exacerbated the neuroinflammatory response to an endotoxin challenge [16–20]. Lipopolysaccharide (LPS), a gram-negative bacterial cell surface proteoglycan, known also as bacterial endotoxin, has been widely used to activate the innate immune response in both the periphery and the brain [21]. The LPS model is particularly relevant to examine activation of brain innate immunity, since it specifically and directly targets microglia, the immune resident cells in the brain [22]. Indeed, LPS binds to CD14 protein and potently activates toll-like receptor 4, which expression has been demonstrated *in vivo* in microglia but not in neurons [23]. LPS causes massive resident microglial activation and peripheral leukocyte infiltration into the CNS, accompanied by a robust and transient transcriptional activation of genes encoding pro-inflammatory cytokines, chemokines, prostaglandins (PGs), thromboxanes (Tx) and free radical-generating enzymes (Fig. 2) [24]. Using the LPS model of neuroinflammation, we showed that COX-2 deletion or selective pharmacological inhibition with celecoxib increase neuronal damage, glial activation, and the expression of brain cytokines and ROS-

expressing enzymes, such as the pro-inflammatory cytokine IL-1 β and the p67^{phox} subunit of NADPH oxidase, a major source of superoxide during neuroinflammation [17,20]. COX-2 gene deletion also increases blood-brain barrier (BBB) permeability and leukocyte infiltration [16,17]. Activated microglia and infiltrated leukocytes further amplify the neuroinflammatory response and neuronal damage by releasing TNF- α , IL-1 β , CCL3/ macrophage inflammatory protein 1 α (MIP-1 α), CXCL2/MIP-2 α and the matrix metalloproteinase-3 and -9, all of which had increased expression in the brain of LPS-challenged COX-2 deficient mice compared with their respective wild type controls [16,17,20]. Consistent with these reports, COX-2 deletion exacerbated endotoxin-induced ocular inflammation [19], and selective pharmacological inhibition of COX-2 with NS-398 increased the transcription of inflammatory genes (mPGES-1, TLR2, CD14, MCP-1) in vascular associated brain cells and parenchymal microglia after systemic injection of LPS [18]. These findings in models of primary neuroinflammation describe a different picture from the described role of COX-2 in mediating the progression of ischemic and or/ excitotoxic brain injury [25]. This apparent discrepancy can be explained depending on the cell types involved in the specific injury model. Thus, COX-2, because of its constitutive expression in pyramidal neurons, could mediate injury in models that directly challenge neurons. Consistent with this hypothesis, COX-2 deletion did not affect markers of inflammation and oxidative stress in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) model, which selectively injures neurons [26]. Furthermore, transgenic mice overexpressing human COX-2 via neuron-specific Thy-1 promoter, causing elevated brain PG levels, showed similar neuroinflammatory response and neuronal damage after direct activation of glial innate immunity [27]. Therefore, protective or toxic effect of COX-2 on neuronal viability depends on whether the primary stimulus is inflammatory or excitotoxic and on the cell type targeted (glia/neurons).

These recent findings suggest that COX-2-derived products can mediate a protective effect in the progression and/or the resolution of inflammation in the brain after endotoxin activation of brain innate immunity. In this regard, the recent discovery of novel lipid mediators may underline the mechanical basis for COX-2 anti inflammatory or pro-resolving properties [28,29].

COX-2 derived anti-inflammatory and resolving mediators

In the resolution phase that follows an inflammatory stimulus, inflammation is cleared allowing the tissue to return to a non-inflamed, homeostatic state. Recent evidence indicates that the resolution phase is an active process, mediated by local-acting and specialized lipid mediators with immunoregulatory properties named lipoxins, cyclopentenone PGs, resolvins, and protectins [30]. The synthesis of some of these bioactive lipid mediators that contribute to the resolution of inflammation requires COX-2 activity [31,32]. Cyclopentenone PGs such as PGJ₂ and 15-deoxy- $\Delta^{12,14}$ -PGJ₂ (15dPGJ₂) are non-enzymatic breakdown products of COX-2-derived PGD₂ (Fig. 1 & 2) [29]. Gilroy and colleagues demonstrated that selective COX-2 inhibitors, by blocking the production of COX-2 derived PGD₂ and its metabolite 15dPGJ₂, disturb the resolution phase of inflammation, and delay the return to homeostasis [15]. 15dPGJ₂ has been shown to suppress iNOS activity and the expression of pro-inflammatory cytokines (TNF- α , IL-1 β , IL-6), decrease monocyte migration, and cause polymorphonuclear monocyte and macrophage apoptosis [29,33]. 15dPGJ₂ is also a potent endogenous ligand of peroxisome proliferator-activated receptor γ , an important immunoregulator. Supporting the hypothesis that COX-2 activity is important in the resolution of inflammation, COX-2 deficient mice show increased infiltration of leukocytes, particularly neutrophils, in the brain after central endotoxin challenge [16].

Recently, additional bioactive lipids with anti-inflammatory and pro-resolution properties, generated *via* COX-2 metabolism of the ω -3 polyunsaturated fatty acids (PUFAs) docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), have been characterized [28,34]. The identification of these ω -3 PUFAs-derived anti-inflammatory compounds is especially relevant for CNS inflammation because in brain phospholipids, DHA and AA, are the most abundant PUFAs, particularly in retina and synaptic terminals [35]. Groeger and collaborators discovered new oxo-derivative of ω -3 PUFAs (EFOX), including DHA, that are generated by COX-2 in macrophages activated by phorbol myristic acetate, LPS and interferon- γ (IFN- γ). The study reported that these EFOX dose-dependently reduced the expression of iNOS and COX-2 and also suppressed the production of cytokines (IL-6, MCP-1) and nitric oxide metabolites in the media of monocyte/macrophage cell lines and in primary murine bone marrow-derived macrophages [34]. Interestingly, COX-2 acetylation by aspirin further increased the generation of these mediators. Aspirin irreversibly acetylates COX-1 (at serine residue 530), blocking its activity and the synthesis of PGs and TX, which have pro-inflammatory and pro-thrombotic properties. However, aspirin also acetylates COX-2 (at serine residue 516), switching the synthesis of classical PGs and TX to the synthesis of anti-inflammatory and resolving mediators lipoxins, resolvins and protectins [30].

Lipoxins are generated from AA, resolvins D and protectins from DHA, resolvins E from EPA *via* lipoxygenases (LOX) or concerted action of COX and LOX *via* cell-cell interaction (Fig. 2&3) [29]. However, after aspirin administration, acetylated COX-2 can generate epimers of lipoxins, resolvins or protectins and increase their formation [36], effects that are blocked by selective COX-2 inhibitors [37]. These aspirin-triggered protective mediators share the same biological activity with their analogs selectively formed through the LOX biosynthetic pathway. They regulate the magnitude and duration of inflammation by attenuating neutrophil infiltration, and initiating the clearance of apoptotic leukocytes [29]. Aspirin-triggered resolvins and neuroprotectins have been found in both mouse and human brain; and exert potent biological actions *in vivo* on leukocyte trafficking and on the regulation of cytokine expression by glial cells [38]. Neuroprotectins have demonstrated neuroprotective effects in experimental brain damage, oxidatively stressed retinal pigment epithelial cells, and β -amyloid-induced neurotoxicity in human brain cells [39]. Further studies are needed to examine whether these COX-2-derived protective mediators can be synthesized by inflamed nervous tissues and exert anti-inflammatory effects *in vivo*.

Another ω -3 PUFA, EPA, present at low concentrations in membrane phospholipids, acts as a substrate for COX-2 for the synthesis of an alternative family of eicosanoids called 3 series-PGs and TX, which are typically less potent than their AA-derived counterparts, because they act as weak agonists at their respective eicosanoid receptors (Fig. 3) [40].

COX-1 is an important player during neuroinflammation

COX-1 recently emerged as a prominent player in CNS neuroinflammation [7,16,17,24,41–44]. In aged rats, brain levels of COX-1-derived TXB₂ and COX-1 expression in the hippocampus are increased and may contribute to the increased brain susceptibility to inflammation and neurodegenerative diseases. Indeed, COX-1 has been shown to support inflammatory processes and facilitate pro-inflammatory PG upregulation in several models of neuroinflammation [16,17,24,42,43,45]. Owing to its predominant localization in microglia, brain immune resident cells, COX-1-derived products seem to be particularly important in modulating the initial phase of the inflammatory response. A recent study also identified COX-1 expression in perivascular cells (a subset of brain resident macrophages), where its expression was increased in response to a systemic LPS challenge, suggesting a

role for COX-1 in mediating the immune-to-brain signaling [7]. Our group showed that COX-1 deficient mice have a decreased inflammatory response, leukocyte infiltration, oxidative stress and neuronal damage after central injection of LPS or A β ₁₋₄₂ [16,24,42], and these effects were associated with altered PG levels. LPS or A β ₁₋₄₂ -induced upregulation of brain PGE₂, PGF_{2 α} and TXB₂ was reduced by genetic deletion of COX-1 and by SC-560, a selective COX-1 inhibitor [24,42]. In agreement with these results, Matousek and collaborators recently demonstrated that COX-1 expression and PGE₂ were upregulated up to 2 months following a sustained IL-1 β overexpression, a model of chronic neuroinflammation, and COX-1 genetic deletion or pharmacological inhibition completely abrogated IL-1 β -mediated PGE₂ increase [43]. Thus, COX-1 seems to play a role not only in acute but also in chronic neuroinflammatory conditions. In this regard, in a mouse animal model of Parkinson's disease, associated with astrogliosis, microglia activation, inflammation and neurodegeneration, COX-1 expression was increased and COX-1 inhibition ameliorated mice survival [44]. Moreover, COX-1 inhibition or genetic deletion attenuated BBB disruption during TNF- α - or LPS-induced neuroinflammation [16,45]. The exact mechanisms by which COX-1 is involved in neuroinflammation remain to be elucidated. Because COX-1 is predominantly present in microglia and perivascular cells, it can be hypothesized that the enzyme can be mobilized within seconds to minutes after an acute challenge, thereby contributing to the local eicosanoid pool at the site of inflammation, even before the induction of COX-2 expression (Fig. 2).

Overall, recent data imply that COX-1 plays a critical role in the process of neuroinflammation and neurodegeneration and that COX-2 may mediate either a neurotoxic or an anti-inflammatory role depending on the stimulus, the cell type targeted by the insult and the substrate used for eicosanoid synthesis.

Therapeutical implications for managing neuroinflammation in neurological and neurodegenerative disorders

It is becoming clear that neuroinflammation, mediated predominantly by microglia, represents an important component of several neurodegenerative diseases and may contribute to cognitive impairment in the elderly. Supporting this concept, several observational studies have shown that long term use of non-steroidal anti-inflammatory drugs (NSAIDs) reduces the incidence of AD and age-related dementia [46,47]. However, treatment trials or secondary prevention trials, mostly using selective COX-2 inhibitors, in AD patients with mild to moderate cognitive impairment failed to show any benefit, except for a small trial with indomethacin, a COX-1 preferential inhibitor [46,48]. The discrepancy between the epidemiological studies and the clinical trials may be ascribed to several reasons, including timing of administration, off-target effects, and selectivity of the NSAIDs used. One possible explanation for the failure of clinical trials is that targeting COX-2 after the onset of dementia, when the inflammatory cascade has already started, is not effective, and treatment should begin before the onset of AD symptoms. Indeed, the first and only primary prevention trial (ADAPT) to test the effect of celecoxib (a selective COX-2 inhibitor) and naproxen (a mixed COX-2/COX-1 inhibitor) on AD incidence did not show any reduction in AD risks, and even suggested detrimental effects on cognitive function in the treated groups compared to placebo [49,50]. Because of cardiovascular safety concerns, the drugs were stopped when the average treatment duration was two years. However, subjects were then followed for two more years. After exclusion of individuals with baseline cognitive syndromes, the later hazard ratio for the naproxen-treated group was significantly reduced (0.33; 95% CI 0.11 – 0.98). A neuroprotective effect of naproxen was also evident in CSF, where the tau/A β ratio was reduced by more than 40% in the group originally assigned to naproxen. This effect was unabated 41 months following treatment termination,

and it remained apparent in a smaller sample of CSF collected an average 13 months after the first. None of these results were seen in those assigned to celecoxib (John Breitner, personal communication). While these findings deserve further investigation, they suggest that NSAIDs can accelerate AD pathogenesis in patients with relatively advanced disease, but naproxen appears to protect against neurodegeneration and incidence of dementia in the subset of patients with healthier brains. Thus, a single agent produced contrasting effects at different stages of AD pathogenesis.

The different distribution patterns of COX-1 and COX-2 expression in the AD brain could implicate that these enzymes are involved in different cellular processes in the pathogenesis of AD. Indeed, COX-1 is predominantly expressed by microglia in rodent and human brain [6] and may be involved in the neuroinflammatory process associated with AD. COX-1 expressing microglia surround amyloid plaques and are increased during AD [6,8]. In contrast, COX-2 expression has not been detected in microglia or astrocytes in the AD brain. Thus, we propose that the beneficial effects of NSAIDs in preventing AD could be due to the inhibition of COX-1 rather than COX-2. An increase in COX-1 expressing microglia and/or COX-1 expression has been observed also in other neurological diseases with a marked inflammatory component, such as traumatic brain injury, Creutzfeld-Jacob disease, HIV-related dementia, and Parkinson's disease, where COX-1 expression often correlated with microglia activation, disease severity and tissue damage (reviewed in [41]).

On the other hand, the discovery of novel COX-2-derived lipid mediators with pro-resolving properties suggests that inhibiting COX-2 could be detrimental in certain neuroinflammatory conditions. Selective COX-2 inhibitors (coxibs) were developed and preferred to classical, mixed NSAIDs because of the lower gastrointestinal toxicity, attributed to the inhibition of COX-1-derived PGs. However, animal studies have shown that specific inhibition of COX-1 alone does not alter gastric or intestinal mucosal integrity, and gastrototoxicity was observed when both COX-1 and COX-2 were inhibited [51–53]. Unfortunately, the failure of the clinical trials with COX-2 selective inhibitors has hindered appropriate follow up on the potential use of COX-1 preferential inhibitors. The only clinical trial with low dose aspirin treatment over 2 years (AD2000) did not demonstrate any benefit in patients with mild to moderate probable AD, and reported hemorrhagic adverse events due to aspirin intake [54]. Low dose aspirin, within the range used for cardiovascular protection, is indeed associated with gastroduodenal toxicity, but several trials have shown that gastric side effects can be countered by concomitant use of proton pump inhibitors [55].

In summary, identifying the specific roles of COX-1 and COX-2 in CNS inflammation and their coupling to downstream receptors could lead to revisit current therapeutic strategies and open new approaches for the treatment of neuroinflammatory conditions. COX-1, traditionally considered merely as the homeostatic isoform, is instead actively involved in brain injury induced by pro-inflammatory stimuli such as A β , LPS, IL-1 β and TNF- α . On the other hand, a major breakthrough in the lipid field has uncovered novel COX-2 derived lipid mediators with anti-inflammatory and pro-resolution properties, which may underlie recent reports demonstrating COX-2 neuroprotective function during neuroinflammatory conditions. Therefore, NSAIDs with higher selectivity for COX-1 rather than COX-2 are more likely to reduce neuroinflammation and should be further investigated as a potential therapeutic approach in neurodegenerative diseases with a marked inflammatory component. The major drawback for the use of selective COX-1 inhibitor was the belief that they will cause more gastrointestinal toxicity than selective COX-2 inhibitors. It is now generally admitted that both COX-1 and COX-2 inhibition are required to elicit NSAID-induced gastric injury. As for many other drugs, the ratio benefit/risk should be weighed. Moreover, the novel pro-resolving functions of COX-2-derived mediators in the termination of inflammation should be considered in the design of innovative anti-inflammatory therapies.

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Fig. 1. The metabolic pathway of arachidonic acid (AA)

AA is released from membrane phospholipids by a phospholipase A₂ (PLA₂) enzyme and metabolized by COX-1 or COX-2 into PGH₂ which is further converted to prostaglandins and thromboxanes by specific terminal synthases. AA can also be metabolized to leukotrienes through lipoxygenases, and to epoxyeicosatrienoic acid (EET) and dihydroxyacids through cytochrome p450 epoxidase. The cyclopentenones PGJ₂ and 15d-PGJ₂ are non-enzymatic degradation products of PGD₂.

Fig. 2. COX-1 and COX-2 distinct roles during the progression of neuroinflammation

Inflammatory stimuli target primarily microglia, the immune resident cells of the brain. They activate pro-inflammatory signaling pathways (NF κ B, STAT/JAK) as well as the AA cascade, leading to the release of cytokines, chemokines, reactive oxygen species (ROS), prostaglandins (PG) and thromboxanes (TX). Being predominantly expressed by microglia, COX-1 contributes within seconds to minutes to the local eicosanoid pool at the site of inflammation, before the induction of COX-2. Chemokines and eicosanoids attract leukocytes and later monocytes to the site of inflammation. During the normal progression of neuroinflammation, resolution occurs with a shift from pro-inflammatory eicosanoids to anti-inflammatory cyclopentanone PGs (PGD₂ and 15-dPGJ₂) synthesis. Cyclopentanone PGs attenuate the induction of inflammatory genes. With time, a class switching occurs towards pro-resolving lipid mediators generated by aspirin-acetylated COX-2 and lipoxygenases (LOX) such as (AA)-derived lipoxins and DHA-derived resolvins and neuroprotectins. DHA can also be directly metabolized by COX-2 into anti-inflammatory oxo-derivatives (13-EFOX) in activated macrophages.

Fig. 3. COX-2 derived novel protective lipid mediators

By acetylating COX-2, aspirin inhibits the synthesis of prostaglandins and thromboxanes from AA or EPA, and triggers the generation of epimeric forms of lipoxins (from AA), resolvins E (from EPA), resolvins D and neuroprotectins (from DHA), *via* lipoxygenases. COX-2 can also directly metabolize DHA to anti-inflammatory oxo-derivatives (13-EFOX), with 17-EFOX being the aspirin-triggered form. 15R-HETE: 15R-hydroxy-eicosatetraenoic acid; 18R-HEPE: 18R-hydroxy-eicosapentaenoic acid; 17R-HDHA: 17R-hydroxy-docosaheptaenoic acid.