Biochimie 93 (2011) 46–51

Contents lists available at ScienceDirect

Biochimie

journal homepage: www.elsevier.com/locate/biochi

Review

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

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ARTICLE INFO

Article history:
Received 7 June 2010
Accepted 14 September 2010
Available online 22 September 2010

Keywords:
Cyclooxygenase
Neuroinflammation
Prostanoids
Neuroprotection
Microglia
Brain

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 discuss 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 review recent data demonstrating that COX-1, classically viewed as the homeostatic isoform, is actively involved in brain injury induced by pro-inflammatory stimuli including Aβ, lipopolysaccharide, IL-1β, 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.

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1. 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) was 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 A_2 (PLA_2), into bioactive prostanoids. Both COX isoforms catalyze the same reactions: dioxygenation of arachidonic acid (AA) to yield prostaglandin G_2 (PGG_2), and a peroxidase reaction, which converts PGG_2 to prostaglandin H_2 (PGH_2). PGH_2 is then transformed into PGE_2, $PGF_{2\alpha}$, PGD_2, PGI_2 and TXB_2 by 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 homodimer 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 by various inflammogens [2]. Indeed, COX-2 gene has several transcriptional regulatory elements, including NF-κB, 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 thought to be the only isoform responsible for propagating the inflammatory response and thus, 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

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0300-9084/$ – see front matter Published by Elsevier Masson SAS.
doi:10.1016/j.biochi.2010.09.009

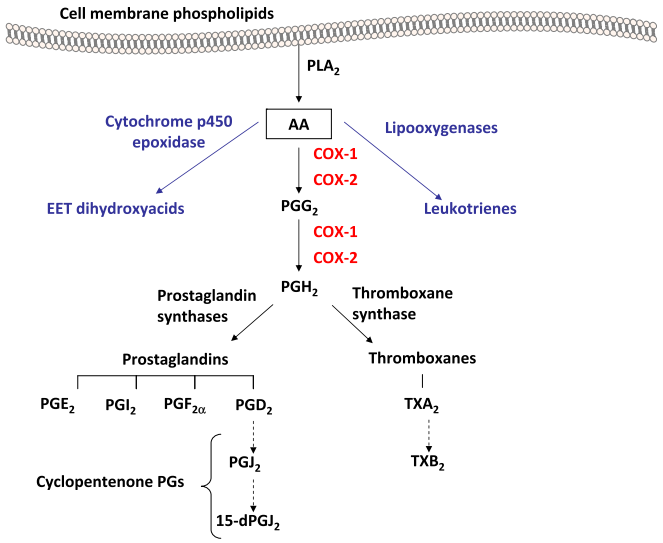

Fig. 1. The metabolic pathway of arachidonic acid (AA). AA is released from membrane phospholipids by a phospholipase A_2 (PLA_2) enzyme and metabolized by COX-1 or COX-2 into PGH_2 which is further converted to prostaglandins and thromboxanes by specific terminal synthases. AA can also be metabolized to leukotrienes through lipooxygenases, and to epoxyeicosatrienoic acid (EET) and dihydroxyacids through cytochrome p450 epoxidase. The cyclopentenones PGJ_2 and 15d-PGJ_2 are non-enzymatic degradation products of PGD_2.

is not surprising that in the central nervous system (CNS) COX-2 is involved 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, PGE_2 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].

2. 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 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]. 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 model of LPS-induced 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-inflammatoy cytokine IL-1β 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-1β, CCL3/macrophage inflammatory protein1α (MIP-1α), CXCL2/MIP-2α 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 show 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. Because of its constitutive expression in pyramidal neurons, COX-2 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].

3. 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]. Cyclopentanone PGs such as PGJ_2 and 15-deoxy-$\Delta^{12,14}$-PGJ_2 (15dPGJ_2) are non-enzymatic breakdown products of COX-2-derived PGD_2 (Figs. 1 and 2) [29]. Gilroy and colleagues demonstrated that selective COX-2 inhibitors, by