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Cyclooxygenase-2 in Synaptic Signaling

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Abstract

Cyclooxygenase-2 (COX-2), a rate-limiting enzyme converting arachidonic acid to prostaglandins and a key player in neuroinflammation, has been implicated in the pathogenesis of neurodegenerative diseases such as multiple sclerosis, Parkinson's and Alzheimer's diseases, and in traumatic brain injury- and ischemia-induced neuronal damage, and epileptogenesis. Accumulated information suggests that the contribution of COX-2 to neuropathology is associated with its involvement in synaptic modification. Inhibition or elevation of COX-2 has been shown to suppress or enhance excitatory glutamatergic neurotransmission and long-term potentiation (LTP). These events are mainly mediated via PGE_2, the predominant reaction product of COX-2, and the PGE_2 subtype 2 receptor (EP_2)-protein kinase A pathway. Recent evidence shows that endogenous cannabinoids are substrates for COX-2 and can be oxygenated by COX-2 to form new classes of prostaglandins (prostaglandin glycerol esters and prostaglandin ethanolamides). These COX-2 oxidative metabolites of endocannabinoids, as novel signaling mediators, modulate synaptic transmission and plasticity and cause neurodegeneration. The actions of these COX-2 metabolites are likely mediated by mitogen-activated protein kinase (MAPK) and inositol 1,4,5-trisphosphate (IP_3) signal transduction pathways. These discoveries suggest that the contributions of COX-2 to neurotransmission and brain malfunction result not only from its conversion of arachidonic acid to classic prostaglandins but also from its oxidative metabolism of endocannabinoids to novel prostaglandins. Thus, elucidation of COX-2 in synaptic signaling may provide a mechanistic basis for designing new drugs aimed at preventing, treating or alleviating neuroinflammation-associated neurological disorders.

Keywords

Inflammation; Prostaglandin E_2; Endocannabinoids; Prostaglandin glycerol esters; Prostaglandin ethanolamides; Synaptic plasticity

Introduction

Neuroinflammation is a biological immune response to various endogenous and exogenous stimuli in the nervous system. However, chronic neuroinflammation may lead to dysfunction in neural circuits and neurological disorders. As a key player in inflammation, the role and mechanisms of cyclooxygenase-2 (COX-2) in neurological disorders are being unraveled. In particular, recent progress on COX-2 as an important mediator participating in excitatory glutamatergic synaptic transmission and long-term synaptic plasticity greatly advances our understanding of mechanisms underlying COX-2-mediated physiological and pathological functions in the brain. As an inducible isoform, the expression and activity of COX-2 are markedly elevated by a wide variety of stimuli ranging from proinflammatory insults and

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epileptic activity to the activation of NMDA receptors [1–5]. This means that synaptic efficacy will be altered when COX-2 is upregulated in neuroinflammation. Nevertheless, the COX-2-mediated synaptic modification is ultimately attributed to the amount of prostaglandins synthesized and their functional receptors. Thus, in this review, we will discuss the most recent information on COX-2 and its reaction products, prostaglandins, in synaptic signaling.

COX-2 in neural plasticity

It has been well documented that cyclooxygenases (COX) catalyze the first committed step of the conversion of arachidonic acid (AA) into unstable intermediate PGG_2, which is rapidly converted to PGH_2 by COX. Finally, a series of biologically active prostaglandins (PGD_2, PGE_2, $PGF_{2\alpha}$, and PGI_2) and thromboxane A_2 (TXA_2) are formed from PGH_2 by various isomerases. Two isozymes of COX, COX-1 and COX-2, have been identified [3,6–11]. COX-1 and COX-2 are membrane-associated enzymes with a 71 kD molecular weight and a 63% amino acid sequence identity [11,12]. COX-1 is constitutively expressed in most tissues of the brain, and its reaction products are expected to mainly contribute to normal physiological function. COX-2 is also constitutively expressed in the CNS (neurons, astrocytes, microglia and endothelia), but enriched in the hippocampus and cortex [1]. Importantly, COX-2 as an inducible enzyme is responsible for the ‘pathological’ production of PGs in response to a variety of stimuli ranging from proinflammatory factors (e.g., cytokines, endotoxin), seizure activity, brain injury, growth factors to the activation of NMDA receptors [1–3,10,11]. Most commonly used non-steroidal anti-inflammatory drugs (NSAIDs) such as indomethacin and aspirin are nonselective and inhibit both COX-1 and COX-2, whereas selective COX-2 inhibitors (Celecoxib, NS398, Vioxx, Valdecoxib) preferentially inhibit COX-2 over COX-1. A putative third isoform, COX-3, was recently reported to be expressed in the canine cerebral cortex and is targeted by acetaminophen [13]. It is a splice variant of the COX-1 transcript and therefore not a new isoform of COX [14,15].

Because of a higher level of COX-2 expression in hippocampal and cortical neurons involved in cognitive function, investigators speculated that COX-2 might participate in neural plasticity. Yamagata et al. [1] provided the initial evidence that the basal expression of COX-2 is regulated by NMDA receptor-dependent synaptic activity. Also COX-2 expression is upregulated by high-frequency stimulation (HFS) associated with the induction of long-term potentiation (LTP), a form of synaptic plasticity and cellular model of learning and memory [16]. This information suggests that the expression level and activity of COX-2 may be linked to long-term synaptic plasticity. This speculation was confirmed by the experiments where authors observed that selective COX-2 inhibitors, but not those of COX-1, reduce HFS-induced LTP at hippocampal perforant path-dentate granule cell synapses [17]. This study provided the first direct evidence that COX-2 is involved in hippocampal long-term synaptic plasticity. The involvement of COX-2 in hippocampal LTP has been confirmed by studies performed by others who show that the inhibition of COX-2 suppresses both LTP [18,19] and long-term depression in the hippocampus [18]. Introducing a small RNA interference (siRNA) technique in conjunction with local electroporation targeting the brain region, Akaneya and Tsumoto [20] reported that the knockdown of COX-2 in the visual cortex significantly decreases the expression levels of COX-2 and almost completely blocks theta-burst stimulation (TBS)-induced LTP, while the gene silencing for COX-1 does not induce significant effects on the induction or maintenance of LTP. This is consistent with the results reported by Chen and Bazan [21], who demonstrated that hippocampal perforant path LTP in COX-1 knockout mice is normal when compared to that in wild type controls. These findings based on the inhibition of COX-2 by selective COX-2 inhibitors or suppression of the COX-2 gene indicate that the constitutively expressed COX-2 participates in long-term synaptic plasticity. To determine whether the inducible form of COX-2 also contributes to synaptic transmission and plasticity, Sang et al. [4] administrated lipopolysaccharide (LPS) or interleukin-1β (IL-1β),

proinflammatory factors, in hippocampal neurons in culture to elevate COX-2 expression and observed that the elevation of COX-2 enhances the frequency of miniature excitatory postsynaptic currents (mEPSCs). Recently, this team revealed that *in vivo* injection of LPS, which elevates COX-2 expression and activity, significantly facilitates basal synaptic transmission and mEPSCs and induces a time-dependent augmentation of LTP at the hippocampal perforant path [5]. Meanwhile, they also showed that hippocampal LTP is potentiated in neuronal COX-2 expression transgenic mice [22]. However, they did not find a significant difference in HFS-induced LTP between COX-2 knockout and wild type control animals [5]. This is probably due to compensatory response by COX-1 in COX-2 null mice [23,24]. These findings suggest that both constitutive and inducible COX-2 play an important role in refinement of synaptic activity [25]. The participation of COX-2 in synaptic transmission and plasticity is supported by the evidence that COX-2 is localized in neuronal dendritic spines, specialized structures where synaptic signaling occurs [4,26,27]. In addition, the involvement of COX-2 in long-term synaptic plasticity and cognition has been supported from the behavioral tests where administration of COX-2 inhibitors impairs passive avoidance task [28,29], memory acquisition, memory retention [30,31], and spatial memory consolidation [32,33]. Since COX-2 plays a key role in neuroinflammation, which is closely associated with brain injury and certain neurologic disorders such as multiple sclerosis, epilepsy, Parkinson's and Alzheimer's diseases [2,15,34–43], an elucidation of COX-2 in excitatory glutamatergic synaptic transmission and plasticity has greatly advanced our understanding of mechanisms responsible for the occurrence of these neurological disorders. For instance, the elevation of COX-2 expression and activity enhances excitatory glutamatergic neurotransmission [4,5]. Glutamate is an important neurotransmitter for cell-to-cell communication under physiological conditions. However, an excessive release of glutamate will induce synaptic dysfunction, neuronal injury, or death. This can be used to explain why chronic neuroinflammation leads to neurodegeneration. Therefore, the information gained from the experiments on the contribution of COX-2 to long-term synaptic plasticity and cognitive function may help in the discovery of ways to prevent and treat neurological and psychiatric disorders resulting from excessive expression of COX-2.

PGE_2 is an important signaling mediator in COX-2-mediated synaptic modification

Cyclooxygenases are the enzymes catalyzing AA into PGG_2/PGH_2, and finally into prostaglandins by cell-specific synthases [3]. Therefore, COX-2-mediated synaptic modification relies on its reaction products, prostaglandins [25]. Both COX-1 and COX-2 are capable of converting AA into five primary prostaglandins (PGD_2, PGE_2, $PGF_{2\alpha}$, PGI_2, and TXA_2), but they exhibit preferentially in synthesizing prostaglandins. It has been demonstrated that PGE_2 and PGI_2 are mainly derived from the COX-2 pathway [4,21,44,45]. To determine which prostaglandin(s) is (are) the signaling mediator(s) responsible for the COX-2-involved modification of synaptic efficacy, Chen et al. [17] examined the individual effects of PGD_2, PGE_2, and $PGF_{2\alpha}$ on the COX-2 inhibitor-induced reduction of hippocampal LTP. It appeared that the COX-2 inhibitor-induced reduction of LTP could be reversed by exogenous application of PGE_2 but not by PGD_2 or $PGF_{2\alpha}$ [17]. This means that PGE_2 may be an important signaling molecule in COX-2-mediated modulation of hippocampal synaptic transmission and plasticity [4,17,21,46]. Further studies revealed that endogenous PGE_2 regulates membrane excitability and synaptic transmission in hippocampal CA1 pyramidal neurons [46]. Under the condition of depletion of endogenous PGE_2, membrane input resistance and frequency of firing were significantly reduced. Meanwhile, exogenous application of PGE_2 reversed this reduction of membrane excitability both in soma and apical dendrites of rat hippocampal CA1 pyramidal neurons. Likewise, exogenous application of PGE_2 produced a greater enhancement of EPSPs and temporal summation in slices where endogenous PGE_2 had been eliminated with NS938

compared with those in control slices. This is the first demonstration that endogenous PGE_2 plays an important role in dynamically maintaining membrane excitability, synaptic transmission, integration, and plasticity in the hippocampus [46]. Akaneya and Tsumoto [20] also provide evidence that PGE_2 serves as a messenger in COX-2-mediated synaptic modulation. They showed that the application of PGE_2 induces a dose-dependent facilitation of TBS-induced LTP, while PGD_2, $PGF_{2\alpha}$, PGI_2, and TXA_2 fail to facilitate LTP in the visual cortex. Meanwhile, TBS increases the release of PGE_2; this increase is completely blocked by RNAi silencing of the COX-2 gene [20]. COX-2 has been shown to be colocalized with PSD-95, a postsynaptic marker, but has little overlap with synaptophysin, a presynaptic marker, confirming the presence of COX-2 in postsynaptic dendritic spines [4,26,27]. This suggests that postsynaptic dendritic spines are an important source of PGE_2 synthesis.

PGE_2 is produced by prostaglandin E synthase (PGES). Because PGE_2 is lipophilic, it diffuses rapidly once synthesized and activates its specific membrane receptors. Three types of PGES (Figure. 1) are responsible for the conversion of PGH_2 into PGE_2: microsomal PGES-1 (mPGES-1), PGES-2 (mPGES-2), and cytosolic PGES (cPGES). Cytosolic PGES is mainly associated with the COX-1 pathway; mPGES-1, however, is preferentially coupled with COX-2; mPGES-2, a constitutive enzyme initially associated with the Golgi membrane and released into the cytoplasm after N-terminal proteolysis, is coupled with both COX-1 and COX-2 [47–50]. The colocalization of mPGES-1 and mPGES-2 with PSD-95 (a postsynaptic marker) suggests that PGE_2 synthases are expressed in postsynaptic dendritic spines [4]. Since COX-2 is also present in postsynaptic dendritic spines, it is likely that PGE_2 is catalyzed by COX-2 from the AA pathway in the postsynaptic dendritic spines. Thus, the sequential biosynthetic enzymes are present in the same subcellular compartment (postsynaptic dendritic spines), implying that the PGE_2 availability is tightly and efficiently regulated by COX-2. This assumption has been supported by recent studies where the elevation of COX-2 expression or activity induced by LPS or IL-1β enhances expression of mPGES-1 and production of PGE_2, which promotes the probability of synaptic glutamate release in cultured hippocampal neurons [4] and in slices [5]. A blockade of the mPGES-1 has also been shown to reduce the production of PGE_2 when COX-2 expression is elevated [49]. Therefore, new drugs targeting the mPGES may hold great potential as alternatives for traditional NSAIDs and COX-2 inhibitors for alleviating or treating neuroinflammation-associated neurological disorders.

EP_2 mediates the PGE_2-induced synaptic modification

Four subtypes of the PGE_2 receptors (EPs) have been identified and cloned, which have been designated as EP_1, EP_2, EP_3, EP_4, and multiple splicing isoforms of the subtype EP_3 [51–55]. EPs belong to the family of seven-transmembrane-domain G protein-coupled receptors (GPCRs).These EP subtypes exhibit a distinctive signal transduction profile and cellular actions (Figure 1). Activation of EP_1 receptors increases the levels of intracellular Ca^{2+}, which is coupled with the Gq-PLC-IP_3 and protein kinase C (PKC) pathways [56,57]. EP_3 is associated with a pertussis toxin (PTX)-sensitive Gi protein resulting in a decrease of cAMP [51,58]. On the other hand, EP_2 and EP_4 receptors couple with the Gs-cAMP-PKA pathway leading to an increase of cAMP [59–61]. Zhu et al. [62] reported that four subtypes of EPs are heterogeneously expressed both in neurons and astroglial cells in the rodent hippocampus and cortex. They observed that EP_2 and EP_3 are the most abundant EPs expressed in the hippocampus and cortex, while only trace amount of EP_1 and EP_4 are detectable. Interestingly, EP_2 and EP_4 are well merged with synaptophysin (a presynaptic marker), but not PSD-95 (a postsynaptic marker), indicating that these two subtypes of EPs are likely present in presynaptic terminals. This is the first evidence that EPs are physically present in synaptic regions in hippocampal neurons, providing important avenues for PGE_2 signaling in synaptic activity.

The roles of EPs in synaptic transmission and plasticity are being uncovered. It has been shown that an EP_2-like receptor in spinal dorsal neurons may mediate PGE_2-induced increase in membrane excitability and inhibition of glycinergic neurotransmission [63,64]. Activation of EP_3 and EP_4 inhibits the release of γ-aminobutiric acid (GABA) from the GABAergic terminals innervating supraoptic nucleus neurons by the opening of nonselective cation channels [65]. Sang et al. [4] reported that PGE_2 increases excitatory postsynaptic potentials (EPSPs), decreases the paired-pulse ratio (PPR) both at perforant path-granule cell synapses in dentate gyrus and Schaffer-collateral synapses in CA1 area of hippocampal slices, and enhances the frequency of mEPSCs in hippocampal neurons in culture. They further demonstrated that an EP_2 agonist mimics the PGE_2 effect, whereas EP_1 or EP_3 agonist fails to enhance the synaptic transmission both in hippocampal slices and primary cultured neurons. As described above, both EP_2 and EP_4 are associated with the Gs-cAMP-PKA pathway and are expressed in presynaptic terminals [62]. To distinguish the role of EP_2 and EP_4 in mediating the PGE_2-induced facilitation of synaptic transmission, the authors designed an experiment in which EP_2 and EP_4 genes are individually silenced by the siRNA technique in cultured hippocampal neurons. Transiently silencing the EP_2 gene eliminated the PGE_2-enhanced miniature synaptic activity, while inhibiting the EP_4 failed to prevent the PGE_2-induced effect. These results provide the convincing evidence that the efficacy of PGE_2 in modulation of synaptic activity is in its activation of presynaptic EP_2 [4,25]. It is likely that PGE_2, which is produced at and released from the postsynaptic site, acts as a retrograde messenger in excitatory synaptic transmission via a presynaptic EP_2 receptor. A recent study confirmed the role of EP_2 in synaptic transmission and plasticity [20]. Suppressing the EP_2 gene results in an abolishment of TBS-induced LTP in the visual cortex [20]. However, this study found that EP_2 is expressed at postsynaptic sites. This discrepancy in location of EP_2 expression between the two studies may be ascribed to the regional specificity of the hippocampus and visual cortex [20]. The function of other EPs in neural plasticity is still not well understood. Akaneya and Tsumoto [20] reported that suppressing the EP_3 gene in the visual cortex leads to potentiate LTP. This suggests that EP_2 and EP_3 may play an opposite effect in long-term synaptic plasticity. Based on the available information, COX-2-derived PGE_2 in the facilitation of glutamatergic synaptic transmission and long-term plasticity is mainly mediated via the EP_2. The role of other EPs in modulation of synaptic efficacy remains to be determined.

The intracellular signal transduction mechanisms responsible for the PGE_2-mediated synaptic modification are less clear. Chen and Bazan [46] reported that the PGE_2-enhanced EPSPs are partially blocked by a PKA inhibitor. However, the effect is completely blocked in the presence of both PKA and PKC inhibitors in rat hippocampal slices. Further evidence from other studies shows that PKA inhibitors attenuate the PGE_2-enhanced mEPSCs in cultured hippocampal neurons [4]. Since the PGE_2-elevated synaptic activity is mainly mediated by the EP_2, which is linked to the Gs-cAMP/PKA pathway, it is believed that the PGE_2-potentiate neurotransmission is mediated via the EP_2–Gs–cAMP/PKA pathway. Extracellular signal-regulated protein kinase (ERK), p38MAPK, and nuclear factor-κB (NF-κB) have been shown to be involved in the expression COX-2 and production of PGE_2. However, little is known about the role of these signal transduction pathways in the PGE_2-mediated synaptic modification, which warrants for further studies.

Endocannabinoids as important signaling mediators in neurotransmission

Endocannabinoids (eCBs) are endogenous metabolites of eicosanoid fatty acids and have been demonstrated to be lipid signaling mediators capable of binding to and functionally activating two cannabinoid receptors (CB_1 and CB_2) that are targeted by Δ^9-tetrahydrocannabinol (Δ^9-THC), the primary psychoactive ingredient in marijuana [66–73]. Cannabinoid receptors are seven-transmembrane, G-protein-coupled receptors, which are negatively coupled to adenylyl cyclase. The CB_1 cannabinoid receptor was molecularly cloned from rat brain in 1990 [74],

and is present in various mammalian tissues, mostly in the central nervous system, while the CB_2 was identified by sequence homology in 1993 [75], and is most abundant in the immune system. Recent evidence shows that the CB_2 is also present in the brain (astroglial cells and brainstem neurons), suggesting that the CB_2 may be involved in physiological and pathological functions in the brain [76–82].

The discovery of CBRs prompted the search for eCBs. At least five endogenous ligands, 2-arachidonoyl glycerol (2-AG), arachidonoyl ethanolamide (AEA or anandamide), 2-arachidonoylglycerol ether (2-AGE), N-arachidonoyl-dopamine (NADA) and -arachidonoyl-ethanolamine (AE, virodhamine), have been identified [70–72,83–89]. While virodhamine, 2-AGE and NADA are a partial or weak agonist for the CB_1 or CB_2 receptor, and their physiology and pharmacology have not yet been clarified [70,71,90], AEA and 2-AG are the two most studied eCBs and have been demonstrated to be involved in a variety of physiological and pathological processes in mammalian tissue via CB_1 and CB_2 receptors [70–72,90–95]. The eCB signaling system is composed of eCBs, cannabinoid receptors, and the enzymes that synthesize, degrade, and transport them. The production and degradation of 2-AG and AEA are through different pathways [70–72,96]. AEA is the first identified cannabinoid agonist, mainly produced from N-arachidonoylphosphatidylethanolamine (NAPE) by phospholipase D and degraded to AA by fatty acid amide hydrolase (FAAH). Several lines of evidence shows that AEA is a partial CB_1 and a weak CB_2 agonist, and an agonist for the vanilloid receptor [97–100]. 2-AG is the second identified cannabinoid receptor ligand, synthesized from diacylglycerol (DAG) by diacylglycerol lipase and hydrolyzed to AA by monoacylglycerol lipase (MGL). 2-AG has been demonstrated to be the most abundantly endogenous ligand and a full agonist for both CB_1 and CB_2 receptors [70–72,90,94]. 2-AG and AEA are removed from extracellular space through a diffusion-facilitated transporter or uptaken via membrane-associated carrier and simple diffusion [101]. Recent progress reveals that 2-AG and AEA are substrates for COX-2 and can be oxygenated by COX-2 to form new classes of prostaglandins: prostaglandin glycerol esters (PG-Gs) and prostaglandin ethanolamides (PG-EAs) [25,102–105]. This means that there is another pathway in degrading eCBs in addition to their well known hydrolysis pathways.

Several pieces of information indicate that eCBs mainly induce an inhibitory effect on both GABAergic and glutamatergic neurotransmission and neurotransmitter release. Mechanisms underlying eCB modulation of synaptic function are still not clear. Presumably they are related to the cannabinoid modulation of ion channels, including transient A-type K ulchannels and voltage-gated P/Q and N-type Ca^{2+}channels, and activation of MAPK cascades [106–108]. A recent study shows that eCB-mediated synaptic signaling is involved in a Ca^{2+}-induced Ca^{2+} release (CICR) by activating the ryanodine receptor Ca^{2+} release channel [109]. One of the most important breakthroughs in understanding how eCBs modulate synaptic efficacy in the CNS results from the pioneer work by Alger and his colleagues [110,111] and Wilson and Nicoll [112,113], who demonstrated the phenomenon of depolarization-induced suppression of inhibition (DSI). DSI refers to eCB-induced suppression of GABAergic synaptic transmission. In DSI, strong depolarization of a postsynaptic neuron induces a release of signal that acts on the presynaptic CB_1 receptor and transiently inhibits the release of GABA. Thereafter, a similar phenomenon was demonstrated for glutamatergic synaptic transmission and was designated depolarization-induced suppression of excitation (DSE) [70,71,114–116]. Thus, eCBs are proposed to serve as retrograde messengers in modulating both GABAergic and glutamatergic synaptic transmission [11–114,117]. The latest evidence indicates that 2-AG, but not AEA, is likely a signaling molecule in mediating CB_1 dependent DSI or DSE [73,94;118–123]. Also enzymes that synthesize 2-AG are present in postsynaptic dendritic spines, providing direct evidence that 2-AG is synthesized in postsynaptic sites and acts on presynaptic CB_1 receptors [124,125]. This information suggests that 2-AG plays an important role as a retrograde messenger in modulating synaptic activity.

COX-2 oxidative metabolism of eCBs in synaptic signaling

Endocannabinoids are substrates for a number of fatty acid oxygenases including the cyclooxygenases, lipoxygenases, and cytochrome P450s [105]. As mentioned above, COX-2 is capable of degrading 2-AG and AEA to form new types of prostaglandins. Interestingly, AEA and 2-AG are poor substrates for COX-1, suggesting that COX-2 oxidative metabolism is an important pathway in degrading or inactivating eCBs and may have functional significance in endocannabinoid signaling in synaptic activity. This has been supported by a recent report where the authors demonstrate that a selective COX-2 inhibitor improves functional outcomes, provides neuroprotection, and reduces inflammation in a rat model of traumatic brain injury [126]. These protective effects appear to result from the reduced COX-2 activity and PGE_2, and preserved the levels of 2-AG [126]. The role of COX-2 oxidative metabolism of eCBs has also been supported by studies where the COX-2 inhibition alters eCB signaling in DSI and long-term synaptic plasticity in the hippocampus [19,25,118,127]. Yang et al. [5] demonstrated that the elevation of COX-2 by *in vivo* injection of LPS or overexpression of neuronal COX-2 by a genetic manipulation abolishes DSI at hippocampal perforant path synapses. Conversely, the inhibition of COX-2 by administration of a selective COX-2 inhibitor or deletion of COX-2 gene augments DSI. These discoveries show an important role of COX-2 oxidative metabolism of eCBs in synaptic signaling. As mentioned above, both COX-2 and the enzymes synthesizing 2-AG are present in postsynaptic dendritic spines of excitatory neurons [4,26,124,125]. Importantly, 2-AG is an endogenous natural substrate for COX-2, and COX-2 preferentially oxygenates 2-AG to prostaglandin glyceryl esters (PG-Gs) as it converts AA to classic prostaglandins, whereas the reaction of COX-2 metabolism of AEA to produce prostaglandin ethanolamides (PG-EAs) is relatively slow [105]. The colocalization of COX-2 and 2-AG in the same subcellular space (postsynaptic dendritic spines) allows COX-2 to rapidly and efficiently metabolize 2-AG when COX-2 expression or activity is elevated. Thus, the inhibition of COX-2 prevents the inactivation of eCBs, raising the eCB levels and promoting the eCB-mediated response, whereas the elevation of COX-2 accelerates the metabolism of eCBs, lowering the eCB levels and attenuating the eCB-mediated response. This means that COX-2 oxidative metabolism of eCBs constitutes an important mechanism contributing to COX-2-mediated synaptic modification, and that increases in COX-2 alter synaptic signaling not only through increased production of PGE_2 from AA, but also through the oxidative metabolism of 2-AG to form new types of prostaglandins (Figure 2). Hence, up- or down-regulation of COX-2 expression or activity will significantly influence the COX-2 oxidative metabolism of eCBs and the effects on synaptic activity.

Novel prostaglandins derived from endocannabinoids in synaptic plasticity

Novel prostaglandins derived from 2-AG include PG-Gs (PGE_2-G, PGI_2-G, PGD_2-G, $PGF_{2\alpha}$-G, and TXA_2-G); those derived from AEA include PG-EAs (PGE_2-EA, PGI_2-EA, PGD_2-EA, $PGF_{2\alpha}$ -EA, and TXA_2-EA) [25,102–106]. Both 2-AG- and AEA-derived novel prostaglandins are significantly more stable metabolically than AA-derived classic prostaglandins, implying that COX-2 metabolism of eCBs may provide oxygenated lipids with sufficiently long half-lives to act as signaling mediators in physiological and pathological functions [105]. Although functional roles of endocannabinoid-derived PG-Gs and PG-EAs in the brain have not been well understood, they may represent unique signal mediators with potent activities distinct from their precursors and corresponding AA-derived prostaglandins [14,25,105]. Nirodi et al. [128] showed that the PGE_2-G, a principal COX-2 oxidative metabolite of 2-AG, mobilizes intracellular calcium, triggers IP_3 synthesis, and activates PKC in RAW264.7 macrophage cells, indicating PGE_2-G may be a signaling mediator. Sang et al. [129] provided the first evidence that COX-2 metabolites of eCBs modulate GABAergic receptor-mediated inhibitory synaptic transmission in primary cultured hippocampal neurons. They found that PGE_2-G, a principal COX-2 oxidative metabolite of 2-AG, significantly

increases the frequency of miniature inhibitory postsynaptic currents (mIPSCs). The increase is not blocked by SR141716, a selective CB_1 antagonist, suggesting the PGE_2-G-mediated effect is not via the CB_1. PGD_2-G, $PGF_{2\alpha}$-G and PGD_2-EA also increased the frequency of mIPSCs in a similar way to PGE_2-G, but PGE_2-EA and $PGF_{2\alpha}$-EA did not. These findings indicate that COX-2 oxidative metabolites of eCBs serve as signal modulators in modulating inhibitory synaptic transmission. In a consecutive study, Sang et al. [130] shows that PGE_2-G enhances excitatory glutamatergic synaptic transmission which is CB_1-independent in hippocampal neurons in culture. In particular, they demonstrated that this COX-2 oxidative metabolite of 2-AG induces neuronal injury and apoptosis and potentiates the NMDA-induced neuronal death in a dose-dependent manner. The PGE_2-G-induced neurotoxicity is blocked by APV, an NMDA receptor antagonist or kynurenic acid, a broad spectrum glutamate receptor antagonist, suggesting that the PGE_2-G-induced neurodegeneration results from the elevated release of glutamate. This is the first evidence showing that the COX-2 oxidative metabolite of 2-AG contributes to neurodegeneration. Endocannabinoids have been demonstrated to exert neuroprotection against β-amyloid-, NMDA-, and kainic acid-induced neurotoxicity and traumatic brain injury- and inflammation-induced neuronal damage [82,93,99,131–140]. This means that eCBs as precursors protect neurons from harmful insults while their COX-2 oxidative metabolites may induce neurotoxicity. It is likely that the levels of eCBs are lowered and the levels of COX-2 metabolites of eCBs are elevated when COX-2 is abnormally elevated or activated in neuroinflammation [25]. Thus, some therapeutic benefits of selective COX-2 inhibitors in relieving inflammation-associated disorders may be derived from the preserved eCBs and reduced endocannabinoid oxidative metabolites. This is new evidence for the role of COX-2 in neuroinflammation-associated neurological disorders.

The inhibition of COX-2 in excitatory synaptic response and long-term synaptic plasticity is CB_1-dependent by most recent studies [19,127]. Yang and his colleagues recently provided direct evidence showing that COX-2 oxidative metabolites of eCBs alter hippocampal long-term synaptic plasticity [5]. They observed that PGE_2-G, PGE_2-EA, and $PGF_{2\alpha}$-EA, COX-2 oxidative metabolites derived from eCBs, elevate hippocampal LTP, the effect opposite to that of their parent molecules 2-AG and AEA [5].

The receptors for these novel prostaglandins have not been cloned and remain to be identified. Sang et al. [129] reported that PG-G- and PG-EA-induced effects on inhibitory synaptic transmission in hippocampal neurons are different from those induced by corresponding AA-derived prostaglandins, suggesting that the endocannabinoid oxidative metabolite-induced effects are not mediated via known prostaglandin receptors, instead, mediated by novel receptors (Figure 2). Hence, identification of the receptors for these novel prostaglandins will further our understanding of the actions of these endocannabinoid oxidative metabolites in synaptic function. Also the signal transduction pathways mediating the endocannabinoid-derived COX-2 metabolites in modulation of synaptic transmission and long-term synaptic plasticity are largely unknown. Recent work [129,130] shows that PGE_2-G-enhanced hippocampal GABAergic and glutamatergic synaptic transmissions are not mediated via PKA and PKC pathways, but appear to be mediated through ERK, p38MAPK, IP_3, and NF-κB signal transduction pathways. This finding has been confirmed by more recent work of Yang et al. [5]. They demonstrated that the PGE_2-G-induced increase in hippocampal LTP is attenuated by an IP_3 inhibitor, indicating the involvement of the IP_3-mediated mobilization of intracellular Ca^{2+} in PGE_2-G-induced increase in LTP. In addition, ERK and p38MAPK inhibitors block the PGE_2-G-potenitated LTP. The involvement of ERK and p38MAPK pathways is further supported from the molecular evidence. PGE_2-G induces a time-dependent phosphorylation of ERK and p38MAPK, and this phosphorylation is attenuated by ERK and p38MAPK inhibitors [5]. Although the role of COX-2 oxidative metabolism of eCBs and their metabolites in physiological and pathological functions and the signal transduction mechanisms in the CNS

has not been well characterized, this pioneer work has begun to unravel the functional role of novel prostaglandins derived from eCBs in synaptic transmission and plasticity.

Perspective

In the past decade, significant progress has been made in the elucidation of COX-2 regulation of PGE_2 signaling in synaptic transmission and plasticity. This greatly advances our understanding of basic mechanisms underlying neuroinflammation-associated neurological and psychiatric disorders. The strategy for new drug design has been focused on targeting the downstream of the COX-2 pathways (e.g., mPGES, EPs) after reports of the occurrence of a series of cardiovascular complications in patients receiving COX-2 inhibitors. Recent work on COX-2 oxidative metabolism and their metabolites in modulating neurotransmission and synaptic plasticity may provide new clues to explore novel therapeutic approaches aimed at preventing, ameliorating or treating neuroinflammation-associated neurological disorders resulting from excessive activation of COX-2.

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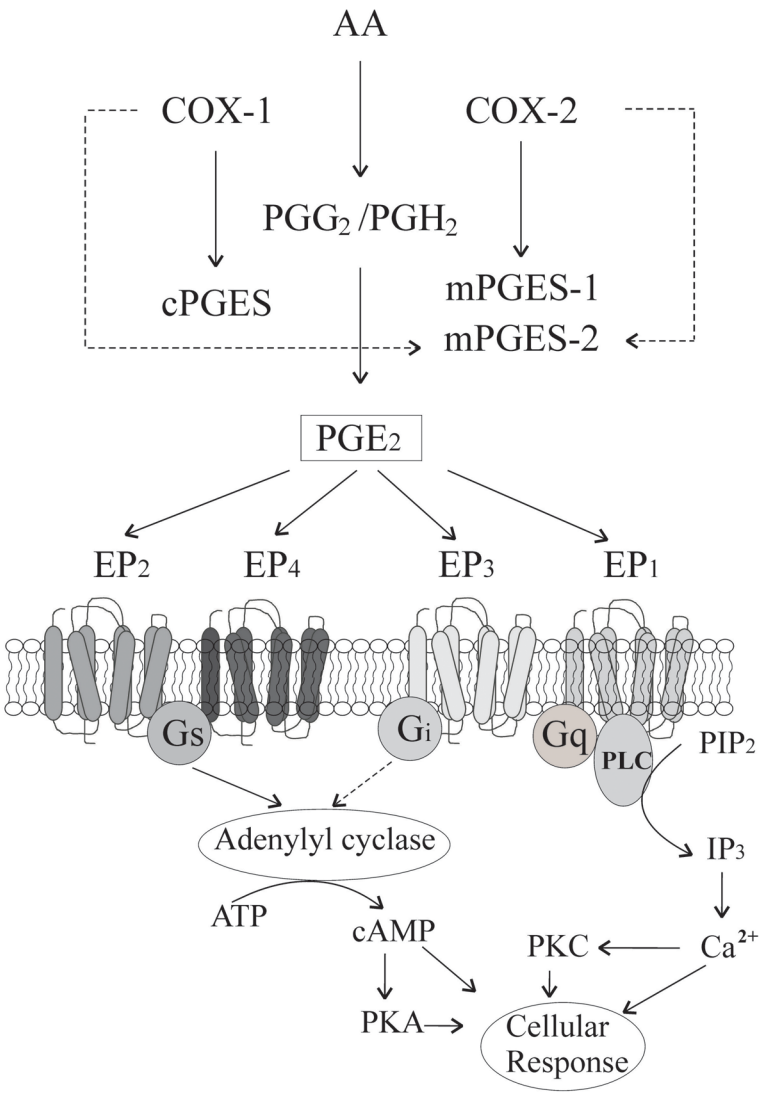

Figure 1.

PGE_2 formation and its signal transduction pathways. Arachidonic acid (AA) is transformed into unstable intermediate PGG_2, which is promptly converted into PGH_2 by cyclooxygenases (COXs). PGE_2 is generated from PGH_2 by cytosolic PGE_2 synthase (cPGES) and membrane-bound PGE_2 synthase-1 and -2 (mPGEs-1 and -2). Cytosolic PGES is mainly involved in COX-1, mPGES-1, however, is preferentially coupled with COX-2, and mPGES-2 is linked with both COX-1 and COX-2. Once synthesized, PGE2 diffuses immediately and activates its specific membrane receptors ($EP_{1–4}$), which belong to the family of seven transmembrane-segment G-protein-coupled receptors. EP_1 receptors couple with the Gq-phospholipase C (PLC)-inositol trisphosphate (IP_3) pathway and its activation results in the release of intracellular Ca^{2+}. EP_2 and EP_4 receptors couple with the Gs-adenylyl cyclase (AC)-cAMP-protein kinase A (PKA) pathway. EP_3 couples with a pertussis toxin–sensitive Gi protein to inhibit AC resulting in a decrease in cAMP.

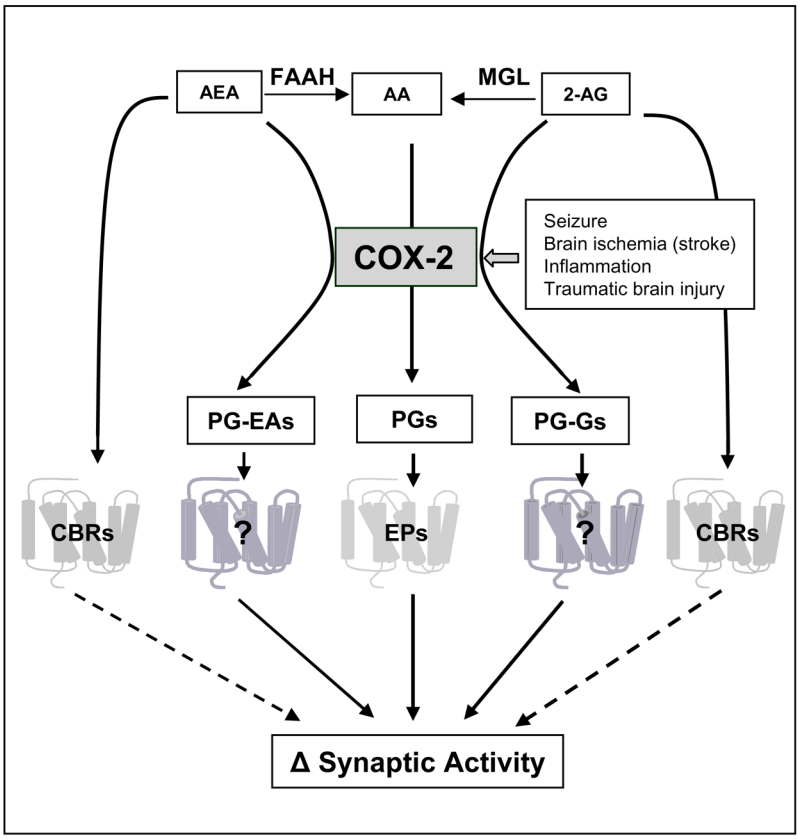

Figure 2.

Scheme illustrating COX-2 oxidative metabolism of arachidonic acid and endocannabinoids in synaptic signaling. Neuroinflammation, brain ischemia, epileptic activity and traumatic brain injury elevate COX-2 expression and activity, which oxygenates AA, 2-AG and AEA to produce prostaglandins (PGs), and PG-Gs and PG-EAs. PGs (mainly PGE_2) facilitate excitatory glutamatergic synaptic transmission via acting on the PGE_2 receptors (EPs, mainly EP_2). Endocannabinoids (2-AG and AEA) activate the presynaptic CB_1 receptors and inhibit the release of neurotransmitters (GABA or glutamate depending upon the types of synapses). COX-2 oxidative metabolites of 2-AG or AEA (PG-Gs or PG-EAs) may exert their role in modulating synaptic events via unidentified receptors (novel receptors?). 2-AG and AEA are also hydrolyzed by MGL or FAAH to AA. 2-AG: 2-arachidonoylglycerol; AEA: arachidonoyl ethanolamide; MGL: monoacylglycerol lipase; FAAH: fatty acid amide hydrolase; AA: arachidonic acid; PGs: prostaglandins; PG-Gs: prostaglandin glycerol esters; PG-EAs: prostaglandin ethanolamides; EPs: prostaglandin receptors; CBRs: cannabinoid receptors