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Prostaglandin E₂ synthases in neurologic homeostasis and disease

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Abstract

Prostaglandin E₂ synthases (PGES) currently comprise a group of three structurally and biologically distinct molecules. These enzymes are part of an important and complex paracrine signaling system involved in a wide range of biological processes. This review focuses on the normal physiological and pathological roles of these enzymes in the nervous system. Specific topics include the role of PGES(s) in fever and sickness behavior, inflammatory pain, and neural disease. Although the field is in its early stages, ongoing development of selective PGES inhibitors for possible use in people creates a significant need to more fully understand the biological roles of these important enzymes.

1. Introduction

In the nervous system, prostaglandin E₂ (PGE₂) is recognized as a key player in multiple processes, including fever generation, sickness behavior, and nociception. It also appears to play a role in synaptic transmission and may contribute to neural injury and neurodegeneration. Generated from arachidonic acid by the sequential actions of cyclooxygenases and PGE synthases, PGE₂ interacts with multiple G-protein coupled receptors derived from 4 different genes and splice variants thereof. As a paracrine factor, local production of PGE₂ and expression of specific receptor subtypes on nearby target cells provides a mechanism for its distinct actions. This review focuses on the immediate upstream enzymes that produce PGE₂ and our current understanding of their roles in modulating neural responses and in neurological disease.

2. Prostaglandin E₂ Synthases

Three different enzymes have been identified with the capacity to convert PGH₂, the immediate product of cyclooxygenase, to PGE₂. These include membrane-associated (or microsomal) prostaglandin E₂ synthase-1 and -2 (mPGES-1, mPGES-2), and cytosolic PGES (cPGES). mPGES-1 is a glutathione-dependent enzyme first cloned in 1999 [1]. A member of the MAPEG (membrane-associated proteins involved in eicosanoid and glutathione metabolism) protein superfamily [2], the 16 kDa mPGES-1 is up-regulated in many tissues by proinflammatory cytokines or growth factors [3]. Parallels between the regulation of mPGES-1 and COX-2 and evidence for coupling of their activities [4,5] have led to mPGES-1 being described as the “inflammatory PGES”. Indeed, inhibitors of mPGES-1 are being developed

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that might provide the benefits of selective COX-2 inhibitors without the cardiovascular risk ascribed to inhibition of endothelial prostacyclin [6,7]. Although co-expression of mPGES-1 and COX-2 occurs in many conditions, this is not always the case. For example, in tumor-bearing mice with elevated circulating proinflammatory cytokines and anorexia, hypothalamic expression of COX-2 was significantly elevated relative to control mice whereas mPGES-1 was not [8]. Evidence for distinct signaling pathways leading to mPGES-1 and COX-2 induction is found in a study where phosphatidylinositol 3-kinase inhibition effectively uncoupled co-regulation of the two enzymes in lipopolysaccharide (LPS) treated rat microglia [9]. Additional information about mPGES-1, its role in peripheral inflammatory diseases, and potential as a therapeutic target can be found in a recent review [3].

A cytosolic glutathione-dependent PGES (cPGES), identified in rat brain, was found to be identical to p23, a previously cloned protein associated with hsp 90 [10]. cPGES is expressed in many different tissues and generally viewed as a constitutive activity [10]. This is consistent with *in vitro* cell transfection experiments demonstrating a selective coupling of COX-1 and cPGES activity [10]. However, LPS significantly induced cPGES activity and mRNA levels in brain [10] and there is evidence that association with hsp90 or phosphorylation by casein kinase II modulates cPGES activity [11,12]. In support of the unique regulation of brain cPGES expression, we demonstrated increased levels of cPGES protein 6 and 24 h following intraparenchymal IL-1 β injection [13]. Moreover, cPGES protein levels were increased 4 hours following whole brain radiation exposure [14]. Thus the view of cPGES playing a constitutive role for PGE₂ production must be questioned, at least in brain.

A third PGES isolated from microsomal fractions of bovine heart [15] that is not dependent on glutathione was cloned in 2002 [16]. Structurally distinct from the other isoforms, the 41 kDa mPGES-2 is expressed in a number of tissues, including brain [16]. In contrast to findings with mPGES-1 and cPGES, co-transfection of mPGES-2 with COX-1 or COX-2 in cell culture showed no isoform specific preference for PGE₂ production [17]. In that same work, immunohistochemical evidence for increased mPGES-2 expression in colorectal cancer was provided, however, little evidence for change in mPGES-2 levels was found in other disease states [17].

Mice have been engineered with specific deletions in each of the three identified PGE synthases. Mice lacking mPGES-1 are viable, and have clearly established a role for mPGES-1 in inflammation related pathology [3]. Experiments using such mice to explore the role of mPGES-1 in brain will be described in later sections. Deletion of cPGES is perinatal lethal with poor lung development and growth retardation [18–20]. The lung phenotype is consistent with a defective glucocorticoid response and the role of p23 as a co-chaperone for the glucocorticoid receptor/hsp90 complex. This was verified by examination of glucocorticoid responsive genes in fibroblasts and tissues generated from these mice, as well as direct demonstration of reduced glucocorticoid transcriptional activation using reporter constructs [18,19]. cPGES deletion studies have not been particularly informative about the contribution of this enzyme to PGE₂ synthesis. Although PGE₂ levels were reduced in lung and other tissues in these mice, these findings were confounded by reductions in COX-1 and COX-2 [19,20]. Interestingly, primary fibroblasts from cPGES null mice showed increased PGE₂ production [19]. Finally, mice lacking mPGES-2 showed no specific phenotype and no alteration in tissue levels (including brain) of PGE₂ or deficiencies in LPS stimulated PGE₂ production from macrophages [21]. These results suggest that mPGES-2 is not involved in PGE₂ synthesis; however, they do not eliminate the possibility of tissue specific roles since not all tissues were examined. Along these lines, a small, but significant decrease in mPGES-2 mRNA and protein expression was found in COX-1 mice and COX-2 deficient mice, compared to their respective wild-type controls, without any change in mPGES-1 or cPGES [22,23].

3. Expression of PGES Isoforms in Brain

In addition to brain endothelial cells, which robustly express COX-2 and mPGES-1 following systemic challenge with LPS and other pyrogens ([24]; see section 4), mPGES-1 immunoreactivity has been observed in cortical and hippocampal neurons [25]. In postnatal murine cortical cultures enriched for neurons, mPGES-1 protein levels increased with culture age, paralleling the appearance of synaptic markers such as synaptophysin and GluR1 [26]. cPGES and mPGES-2 proteins were also detected in these cultures; however, their levels did not change with time. Immunohistochemical studies in hippocampal primary neuron cultures revealed co-localization of COX-2 and mPGES-1 with PSD-95, a marker of dendritic spines, and support a role for activity dependent COX-2/mPGES-1 production of PGE₂ in synaptic plasticity [27].

mPGES-1 immunoreactivity has been reported in neurons and microglia following transient forebrain ischemia in mice [28], in microglia and neurons following LPS injection in the rat substantia nigra [29], and in neurons, microglia and some astrocytes in human brain [30]. In culture studies, primary microglia from mouse and rat show robust induction of COX-2 and mPGES-1 expression following LPS stimulation [29,31]. Interestingly, increases in mPGES-1 levels were delayed relative to COX-2 (peak at 24 vs. 12 hours) and were consistent with delays in generation of PGE₂ vs. other prostanoids in the cultures [29]. Although mPGES-2 and cPGES were also expressed by microglia in culture, they were not affected by LPS treatment [29], and did not contribute to PGE₂ production based on experiments with mPGES-1 null microglia or mPGES-1 antisense treatment [29].

In contrast to LPS, treatment of rat microglia with phosphatidylserine (PS) liposomes led to rapid release of PGE₂ with no detectable levels of COX-2 or mPGES-1. Instead, a dramatic increase in mPGES-2 was observed with a smaller increase in cPGES [32]. These findings suggest a COX-1/mPGES-2 (or cPGES) dependent production of PGE₂ in microglia reacting to apoptotic cells. Additional studies with microglia from COX-1 and mPGES-2 null mice would be helpful in confirming these findings. It is worth noting that this pathway may be important for microglial production of PGE₂ since microglia *in vivo* constitutively express COX-1 [33–35].

Using a subtractive hybridization approach, Satoh et al. cloned mPGES-1 from rat astrocytes responding to beta-amyloid [36]. Furthermore, we observed induction of mPGES-1 (and cPGES-1) in primary cultures of mouse astrocytes treated with IL-1 β (unpublished data). Thus, many types of cells in the brain have the capacity to synthesize and regulate production of PGE₂ through expression of the PGES enzymes.

4. PGES in Fever and Sickness Behavior

Nonsteroidal anti-inflammatory drugs (NSAIDs) are used by millions of individuals to reduce fever and discomfort due to bacterial and viral infections. It has long been recognized that their utility is due to reduction of prostaglandin signaling at one or more interfaces between the systemic circulation and brain, particularly the hypothalamus. A detailed discussion of the mechanisms underlying prostaglandin mediated communication between the periphery and central nervous system is beyond the scope of this article and has been recently reviewed [37]. Evidence that mPGES-1 is involved in fever induction includes: 1) demonstration that COX-2 and mPGES-1 are up-regulated in response to pyrogens such as LPS in many tissues [38,39]; 2) co-localization of enhanced COX-2 and mPGES-1 immunoreactivity in brain endothelial cells following LPS and cytokine treatment [24,40]; and 3) abrogation of the febrile response following peripheral LPS challenge in mice lacking mPGES-1 [41]. Importantly, in this last work, mPGES-1 knockout mice were still able to mount a febrile response following intraventricular injection of PGE₂. Fever induced by peripheral injection of IL-1 β or turpentine

was also abrogated in mPGES-1 null mice, indicating the importance of this enzyme in response to systemic immune challenge [42]. In support of a direct role for mPGES-1 mediated PGE₂ generation in signaling to the brain, induction of c-fos immunoreactivity in many brain nuclei, including classic “immunosensitive regions” in the brainstem and hypothalamus, was greatly attenuated in mPGES-1 mice treated with LPS [43]. Finally, a specific inhibitor of mPGES-1 (MF63; 2-(6-chloro-1*H*-phenanthro-[9, 10-*d*]imidazol-2-yl)isophthalonitrile) was recently shown to inhibit fever in LPS treated rodents [6]. Taken altogether, these results strongly support a critical role for mPGES-1 in fever generation.

In addition to fever, other sickness related behaviors have been shown to require mPGES-1 activity. In particular, anorexia following IL-1 β challenge was not seen in mPGES-1 knockout mice [44,45]. Interestingly, in one of these studies, anorexia following LPS challenge was not dependent on mPGES-1 unless mice were prestarved. This suggests additional pathways of signaling for anorexia vs. fever responses in the case of LPS [44]. mPGES-1 has also been shown to be required for tumor-induced anorexia, where inflammatory cytokines are chronically elevated [8]. Interestingly, the authors were not able to demonstrate elevation of mPGES-1 in brain tissue from animals bearing tumors. This contrasts with results seen following acute immune challenge (LPS) and likely reflects the chronic stimulus in the setting of basal brain mPGES-1 expression. The importance of mPGES-1 and PGE₂ in the brain's response to systemic immune challenge was recently shown at the level of the entire hypothalamic-pituitary-adrenal axis with mPGES-1 null mice showing a blunted corticotropin-releasing hormone and impaired glucocorticoid response to LPS [46]. Based on all of these findings, drugs that selectively target mPGES-1 may be useful in reducing the effects of systemic inflammation.

5. PGES in Inflammatory Pain

Drugs that target mPGES-1 may also prove useful for relief of inflammatory pain. mPGES-1 is dramatically up-regulated along with COX-2 in several models of inflammation associated with pain such as carrageenan-induced paw edema [47] and selective inhibition of mPGES-1 with MF63 reduced LPS-induced thermal hyperalgesia in the guinea pig paw as well as dysfunction occurring in a chronic (3 day) model of iodoacetate-induced osteoarthritic pain [6]. Moreover, mice lacking mPGES-1 showed reduced inflammatory pain, measured as number of writhings following intraperitoneal administration of acetic acid [48,49]. Reduced pain behavior was associated with reduced intraperitoneal PGE₂ levels in the knockout mice, consistent with modification of the local inflammatory response and sensitization of nociceptors. Indeed, there was no evidence for modification of normal pain responses in mPGES-1 null mice as assessed by withdrawal latencies using the hot-plate assay [49]. Normal nociceptive responses in mPGES-1 knockout mice were also reported by another group investigating neuropathic pain using L5 spinal nerve transection [50]. However, relative to wild-type mice, animals lacking mPGES-1 did not show thermal hyperalgesia or mechanical allodynia for up to one week following nerve transection [50].

Although these preclinical models support the idea that mPGES-1 might be a useful therapeutic target for inflammatory pain, concerns have been raised about the possibility that mPGES-1 inhibition might redirect prostanoid synthesis to other end-products, some of which are also important modulators of hyperalgesia [51]. There is also some evidence that other PGES isoforms have the capacity to modify pain responses. In particular, downregulation of cPGES expression using intrathecal antisense oligonucleotides in rat spinal cord diminished nociceptive behavior in the acute formalin flinch assay as well as a thermal hyperalgesia test following zymosan injection in the hind paw [52]. These findings suggest that cPGES, possibly linked to COX-1, plays a role in acute spinal nociceptive processing.

6. PGES in Neural Disease

A role for PGE₂ in neural injury has been established in models of ischemic brain injury, amyotrophic lateral sclerosis, Parkinson's disease, and Alzheimer's disease using mice lacking individual PGE receptors [53]. In contrast to these studies and the much larger number of publications relating cyclooxygenase activity to brain injury, ischemia and neurodegenerative diseases, relatively few studies have investigated the role of PGE synthases.

A number of investigators have reported neuroprotection in ischemic injury models with COX-2 inhibitors and specific EP receptor ablation. A clear role for mPGES-1 was demonstrated in brain ischemia using a transient middle cerebral artery occlusion model in wild-type and mPGES-1 knockout mice [28]. mPGES-1 null mice showed no elevated PGE₂ in postischemic cortex at 24 h accompanied by markedly reduced (50% or more) infarct volume, edema, and numbers of TUNEL-positive cells. Ischemia induced changes in two behavioral indices (neurological score and locomotor activity) were similarly reduced in the mutant mice [28]. A direct role for PGE₂ was confirmed by injecting appropriate doses of PGE₂ into the ventricle just prior to ischemic injury. mPGES-1 knockout animals receiving such injections showed worsening of tissue damage and behavioral endpoints to levels like those of wild type mice. In the absence of ischemic injury, PGE₂ had no effect [28]. These findings indicate a critical role for mPGES-1 and PGE₂ in ischemic brain injury, which has also been shown to be responsive to glutamate receptor antagonists. Thus it seems likely that mPGES-1 may also play a role in other damage associated with enhanced excitotoxicity such as neuronal loss following seizures. There is one report of elevated mPGES-1 expression following pilocarpine-induced seizures in rat [54]. However, in contrast to the robust expression of COX-2 in the hippocampus and piriform cortex, mPGES-1 expression was highest in thalamic nuclei. This disconnection between COX-2 and mPGES-1 expression is unusual; however, it should be pointed out that these studies were conducted using *in situ* hybridization and so modest changes in levels of mPGES-1 associated with COX-2 might have been missed. A brief comment in a review article hints that neuronal death following seizure induction with kainic acid is attenuated in mPGES-1 knockout mice [55]; however these findings have not yet been published as a full paper.

COX-2 expression is increased in a wide range of epithelial cancers and a number of investigators have reported elevations in mPGES-1 in cancer, particularly colorectal and lung [3]. mPGES-1 has also been shown to be elevated in a subpopulation of glioblastoma multiforme tumors. Whereas no differences in COX-2 expression were observed between tumor groups, patients harboring tumors with high levels of mPGES-1 showed significantly greater survival [56]. Based on a series of *in vitro* experiments, the authors suggest that increased PGE₂ makes cells more vulnerable to apoptosis through effects on Bax [56].

mPGES-1 levels were found to be elevated in western blots of middle frontal gyrus tissue extracts from Alzheimer's patients relative to age matched controls [30]. The authors report that mPGES-1 immunoreactivity was generally higher in AD patients than controls, particularly in cortical pyramidal cells. Nearly all AD samples were Braak stage VI (end-stage). Interestingly, several investigators have reported decreased expression of COX-2 in end-stage AD, perhaps reflecting a loss of synaptic activity dependent expression [57–59]. Difference in brain regions investigated and types of cases (many in the mPGES-1 study were from familial AD patients) make it impossible to know whether there is a divergence in expression between the two enzymes in AD. The same group has also investigated cPGES expression in AD brain. In contrast to findings with mPGES-1, they reported consistent decreases in middle frontal gyrus neuronal cPGES expression in 10 AD cases vs. 5 control cases [60].

Finally, cyclooxygenase and cPGES expression have been evaluated in brain tissue from patients with psychiatric disease provided by the Stanley Medical Research Institute [61]. Although no clear changes in COX-1 or COX-2 were observed among control brains and samples from patients with bipolar disorder, major depression, or schizophrenia, there was dramatic variation in cPGES expression detected by western blot, with significantly reduced levels observed in all psychiatric disease in frontal lobe samples and in bipolar disease in temporal lobe samples [61]. Interestingly, bipolar patients who were not medicated at the time of death showed the greatest decrease in cPGES expression, though numbers of such individuals were small. Although there is some evidence connecting arachidonic acid metabolism to psychiatric disease, and drug treatment (particularly the mood stabilizers valproate and lithium) to changes in the responsible enzymes [62,63], the meaning of reduced cPGES in psychiatric disease is unclear. Given recent evidence that cPGES (p23) plays an important role in regulating glucocorticoid receptor activity [18, 19], attention should be drawn to the possibility that reduced cPGES levels reflect abnormalities of the HPA axis and hypercortisolism, which have been reported in bipolar disease [64].

7. Conclusions

Generation of PGE₂ is a critical step for cell-cell communication that underlies a wide range of physiologic and pathologic processes. Studies of mice lacking mPGES-1 as well as more recent work with an mPGES-1 inhibitor provide compelling evidence for its role in a variety of normal physiologic responses as well as inflammatory pain and promotion of ischemic brain injury. In most cases COX-2 is also involved, though there are often delays between the peak levels of expression for each of these enzymes. In contrast to most other tissues where it is constitutively expressed, cPGES levels are regulated in brain. The possible multiple actions of cPGES and the perinatal lethality of mice harboring cPGES deletions present challenges for understanding its role in the brain. Future studies using floxed cPGES mice would be of significant value. Given the utility of current NSAIDs and their side effects, continued effort in developing mPGES-1 inhibitors for patient therapy is likely.

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Figure 1.

PGES isoforms are coupled with specific cyclooxygenase activities to generate PGE₂ for constitutive and regulated actions in the nervous system. In the case of mPGES-1 and COX-2 this includes increased expression of the two enzymes in response to inflammatory stimuli (red arrows). The role of mPGES-2 in production of PGE₂ has not been clearly defined *in vivo* (see text).