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Modulation of dendritic cell function by PGE2 and DHA: a framework for understanding the role of dendritic cells in neuroinflammation

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Abstract

Neuroinflammation characterizes various neurological disorders. Peripheral immune cells and CNS-resident glia contribute to neuroinflammation and impact CNS degeneration, recovery and regeneration. Recently, the role of dendritic cells in neuroinflammation received special attention. The function of infiltrating immune cells and resident glia is affected by various factors, including lipid mediators. Polyunsaturated fatty acids, especially n-6 arachidonic acid and n-3 docosahexaenoic acid (DHA), the most abundant in the CNS, play an important role in neuroinflammation. The major arachidonic acid bioactive derivative in immune cells, PGE2, and DHA have been reported to have opposite effects on dendritic cells in terms of cytokine production and activation/differentiation of CD4⁺ T cells. Here we review the existing information on PGE2 and DHA modulation of dendritic cell function and the potential impact of these lipid mediators of dendritic cells in CNS inflammatory disorders.

Keywords

dendritic cells; docosahexaenoic acid; lipid mediators; neuroinflammation; PGE2; T-cell differentiation

Although the degree of peripheral immune cell infiltration into the CNS varies from high in autoimmune multiple sclerosis (MS) and in CNS injuries such as traumatic brain injury, spinal cord injury and cerebral ischemia, to low in Parkinson's disease (PD) and Alzheimer's disease (AD), neuroinflammation is recognized as a feature of virtually all neurological disorders. Peripheral immune cells such as polymorphonuclear leukocytes, dendritic cells (DCs), T and B lymphocytes, as well as CNS-resident cells such as microglia, contribute to neuroinflammation and have an impact on CNS recovery and neuroregeneration. A number of factors including extent, timing, chronicity, localization and type of immune cell influence the detrimental versus beneficial effect of neuroinflammation [1]. These factors can be affected by numerous endogenous and/or exogenous agents, including lipid mediators. A large body of literature addresses the role in inflammation of arachidonic acid (AA) derivatives such as prostaglandins, thromboxanes and lipoxins, and of

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docosahexaenoic acid (DHA) and eicosapentaenoic acid derivatives including resolvins and neuroprotectins [2–5]. The most abundant CNS polyunsaturated fatty acids, AA and DHA, and their bioactive derivatives, especially PGE2 and neuroprotectin D1 (NPD1) have been reported to play an important role in neuroinflammation. Recently, PGE2 and DHA have been shown to have opposite effects on DCs in terms of cytokine production and activation/differentiation of CD4⁺ T cells. Since DCs have been reported to play an important role in CNS trauma and autoimmune disorders [6–10] this article is focused on the modulation of DC function by PGE2 and DHA as it relates to neuroinflammation.

CNS DCs: localization, origin & function

Dendritic cells bridge innate and adaptive immunity and are essential mediators of immunity and tolerance through their ability to present both foreign and self-antigens. DC subsets, distinct in terms of surface markers and function, are present in both lymphoid and nonlymphoid organs. Most DCs are derived from a bone marrow common myeloid progenitor [11]. Recent studies identified the stages of steady-state DC development as a sequence starting with the common myeloid progenitor, followed by macrophage-DC progenitors, and the common DC progenitor [12,13]. Common DC progenitors give rise to plasmacytoid DCs and conventional DC precursors, which leave the bone marrow and enter blood circulation. DC precursors end up in lymphoid and nonlymphoid tissues differentiating into various conventional DC (cDC) subsets. In addition, although blood monocytes are not DC precursors in steady-state, they can acquire cDC features and functions in inflammatory conditions [14,15].

CNS DCs in the steady state

In contrast to most tissues, DCs are rarely detected in healthy CNS. Previous studies reported that in the absence of inflammation, DCs were present only in the vascular-rich areas of the CNS, primarily the meninges and choroid plexus [16–19]. However, the presence of CD11c⁺ DCs in brain parenchyma was reported recently in an elegant study using CD11c/EYFP mice. EYFP⁺ brain DCs (bDCs) were identified in both embryonic and adult CNS in circumventricular organs, which lack a blood–brain barrier (BBB), in regions that receive molecules bypassing the BBB, and in regions that undergo neurogenesis and synaptic turnover [20]. In addition, low numbers of DCs were identified by morphology and MHCII expression in human choroid plexus, and DCs were also identified in human cerebral spinal fluid (CSF) [21,22].

The origin of CNS-derived DCs is still under debate. Resident microglia are a possible source, since *in vitro* experiments showed that microglia can assume a DC phenotype in the presence of GM-CSF [23,24]. The function of steady-state bDCs is still subject to speculation. In the developing CNS, bDCs could be involved in the organization of brain structures through removal of cellular debris. In the adult brain, bDCs could continue to play a role in neurogenesis. Their location in regions involved in postnatal neurogenesis [20], and studies showing the involvement of splenic DCs in the survival and proliferation of neural stem/progenitor cells and in functional recovery following spinal cord injury [25], support an on-going role of bDCs in adult neurogenesis. In addition, the distribution of bDCs in regions of the brain that lack a BBB or along pathways that bypass the BBB and therefore could serve as conduits for pathogens into the CNS parenchyma is in agreement with the well-recognized role of peripheral DCs as immune sentinels.

CNS DCs in inflammatory conditions

In contrast to the steady-state, inflammatory conditions associated with CNS infection, autoimmunity or trauma, result in an increase in the number of DCs in the CNS and in their

expansion into the parenchyma. The development and involvement of CNS DCs, primarily cDCs, has been described in murine models of parasitic and viral infections, and increased numbers of both cDCs and plasmacytoid DCs were reported in the CSF of patients with bacterial meningitis and Lyme meningoencephalitis [26].

Dendritic cells also accumulate in the CNS following injury. In focal cortical ischemia in mice, DCs with a predominant myeloid immature phenotype appeared within 3 days and persisted for 14 days [27]. In a permanent middle cerebral artery occlusion (MCAO) model in rats, activated DCs expressing proinflammatory cytokines accumulated in the ischemic hemisphere within 1 h [28]. Using a transient MCAO model in bone marrow chimeras in CD11c/EYFP mice, Bulloch and colleagues showed DC presence in the infarcted hemisphere within 24 h and established that peripherally derived cDCs populated the infarct core, whereas brain resident bDCs expressing high levels of MHCII and CD80 were localized in the border region in the proximity of incoming T cells [7]. A similar recruitment of both peripheral DCs and resident bDCs in brain parenchyma was reported in the acute kainic acid-induced excitotoxicity model [20,29].

In contrast to infectious diseases and CNS injury models, where the role of CNS DC is still sketchy, significantly more information is available regarding the presence and function of DCs in CNS autoimmunity, such as MS and experimental autoimmune encephalomyelitis (EAE). Although there are differences between MS and EAE, the EAE model provides a much needed tool for dissecting the cellular/molecular processes involved in MS. EAE is a demyelinating CNS disorder mediated by myelin-specific T cells induced in the periphery and reactivated in the CNS. Various T-cell subsets, including Th1-, Th17- and IL-17-producing T $\gamma\delta$ cells have been shown to act as encephalitogenic T cells [30]. Direct involvement of CNS DCs in EAE has been strongly suggested by the increase in DC numbers during acute and chronic disease and their persistence in relapses [23,31,32]. Both myeloid and non-myeloid DCs were found in the CNS of EAE mice [23,31,33,34], and follicular DCs were described in lymphoid-like structures in the meninges of mice with progressive relapsing EAE [35]. In addition, when the numbers of CNS DCs were boosted through systemic Flt-3 administration, there was a substantial increase in EAE clinical symptoms [36]. In MS patients, increased numbers of myeloid and plasmacytoid DCs were found in the CSF, and mature DCs were identified in perivascular cuffs in demyelinated and inflamed lesions [22,37,38].

The role of CNS DCs in EAE/MS appears to be two-fold, inducing local reactivation of encephalitogenic T cells and providing the cytokine environment required for T-cell differentiation and maintenance of specific functional phenotypes. T-cell reactivation occurs in the perivascular space surrounding the microvessels, through interactions with perivascular macrophages and DCs [39,40]. During inflammation, DC transmigration through the BBB in a process that requires both CCL3 and expression of matrix metalloproteinases (MMPs) [41]. Restimulation of encephalitogenic T cells by antigen-presenting cells is required for further transmigration through the glia limitans into the brain parenchyma [36,42]. The role of CNS DCs in T-cell stimulation was confirmed by experiments showing that myeloid DCs and macrophages isolated from the CNS of EAE mice activate naive myelin-specific CD4⁺ T cells *in vitro*, and that priming and differentiation of naive T cells *in vivo* during epitope spreading in relapsing-remitting EAE occurs in the CNS [33,43].

Differentiation into the various effector T-cell subsets is controlled primarily through cytokines produced by local antigen-presenting cells, including DCs. For example, IFN- γ -producing CD4⁺Th1 cells are generated in the presence of IL-12, differentiation of IL-17-producing CD4⁺Th17 requires IL-6, IL-1 and TGF- β well as IL-23 for lineage commitment, and T $\gamma\delta$ cells secrete high levels of IL-17 in the presence of IL-1 and -23, in the absence of

T-cell receptor engagement. Although both Th1 and Th17 can induce EAE, the clinical signs and pathology are different, with predominant monocyte/macrophage infiltration in the spinal cord for Th1, and neutrophil infiltration in the brain for Th17 [44,45]. $\gamma\delta$ cells, producing IL-17 in response to IL-23 and -1 β in the absence of T-cell receptor stimulation, are present at high frequency in EAE brain and in acute brain lesions and the CSF of MS patients [46–48]. Recently, a subset of $\gamma\delta$ cells that express IL-23R constitutively were shown to be the first cells that respond to IL-23 by producing IL-17 and to inhibit the generation and function of Foxp3⁺ regulatory T cells in EAE [49]. Since cDCs produce proinflammatory cytokines including IL-23, -1 β , -12 and -6, they can provide the cytokine microenvironment required for the differentiation of Th1 and Th17, and can activate $\gamma\delta$ directly through the generation of IL-23 and -1 β . A recent report emphasized the important role of CNS DCs in controlling EAE pathogenesis. Intracerebral inoculation of myelin oligodendrocyte glycoprotein-pulsed mature DCs in immunized mice exacerbated disease, inducing an early CNS infiltration of IFN- γ -producing CD4⁺ T cells and a reduction in Foxp3⁺ regulatory T cells. By contrast, inoculation of myelin oligodendrocyte glycoprotein-pulsed semimature DCs prevented or delayed EAE onset, reduced IL-17 and increased IL-10 in the CNS [50]. Taken together, these studies suggest that the activation state of CNS DCs plays an essential role in the activation, differentiation and parenchymal infiltration of autoimmune encephalitogenic T cells.

Modulation of inflammation in brain through lipid mediators

The brain has the second highest lipid content next to the adipose tissue, and lipid metabolism is of particular importance in CNS development, injury and disorders [51–54]. Brain lipids are rather complex, including glycerophospholipids, sphingolipids, gangliosides and cholesterol, and bioactive derivatives, especially of the glycerophospholipid polyunsaturated fatty acids (PUFAs), have been implicated in neuroinflammation in a variety of CNS disorders. The major CNS PUFAs are the n-6 AA and the n-3 DHA derived from the essential fatty acids linoleic acid and α -linolenic acid, respectively. DHA is the predominant component in the gray matter with AA being prevalent in the white matter [55]. In inflammatory conditions, stimuli such as cytokines and chemokines activate phospholipase PLA2 isoforms to release cell membrane PUFAs, which are subsequently metabolized by COX and LOX enzymes to eicosanoids (from AA) and docosatrienes (from DHA) [52,56–60]. In addition, nonenzymatic, free radical-catalyzed peroxidation of PUFAs results in the generation of isoprostanes (AA) and neuroprostanes (DHA) [61,62].

Although the CNS is viewed as a steady-state immune-privileged organ, acute inflammation occurs in pathological conditions in response to infection, injury or autoimmunity, involving primarily resident microglia and recruited peripheral immune cells, which play an essential role in the elimination of pathogens, phagocytosis of apoptotic/necrotic cells and removal of cellular debris [63,64]. Products of AA metabolism, such as prostaglandins, thromboxanes and leukotrienes play a mostly activating role in the acute inflammatory process. The concept of the resolution phase of acute inflammation has changed in the last few years from a passive to an active process involving lipid mediators generated primarily, but not exclusively, from n-3 PUFAs [2,65]. In the brain, docosanoids generated from DHA, as well as lipoxins and PGD2 generated from AA, have been proposed to play a central role in the resolution phase [54,66].

AA derivatives

Arachidonic acid is released in response to physical, chemical or inflammatory agents, initially through the action of PLA2 leading to the generation of proinflammatory prostaglandins, thromboxanes and leukotrienes through reactions catalyzed by COX and LOX (Figure 1) [67,68]. In a second phase, AA release leads to the generation of lipoxins

and of the anti-inflammatory PGD₂ [69]. In addition, eicosanoids such as PGE₂ can also induce changes in lipid profile, reprogramming inflammatory cells to switch from leukotrienes/prostaglandins to the generation of anti-inflammatory lipoxins [70]. The various lipid mediators act through specific receptors and have different biological activities depending on the cell type and signaling pathway.

A number of studies, not always in agreement, reported on the role of the various AA derivatives in inflammatory and neurodegenerative diseases. COX-2 has been shown to be rapidly activated in cerebral ischemia, seizures and neurodegenerative diseases with an inflammatory component such as AD, PD, amyotrophic lateral sclerosis (ALS) and MS [71,72]. Increased PGE₂ levels were reported in the CSF of patients with AD, ALS, ischemic stroke and HIV-associated dementia [73]. In models of ischemic stroke, COX-2 was shown to play a detrimental role. COX-2-deficient mice were more resistant to injury, whereas COX-2 over-expression led to larger infarct volumes [74,75]. In addition, treatment with the COX-2 inhibitor valdecoxib reduced infarct volume, whereas intracerebroventricular injection of PGE₂ had a detrimental effect [76,77]. The fact that mPGES-1-deficient mice showed 50% or more reduction in infarct volume, edema and numbers of TUNEL-positive cells, focused attention on PGE₂ as the major lipid mediator [77]. In mice, neuronal cells in multiple regions of the brain express PGE₂ receptors (EP)1, EP2 and EP3, with EP4 expression restricted to some hypothalamic nuclei. In addition, activated microglia express functional EP2, and inducible EP1 and EP3, and astrocytes express EP2, EP3 (inducible) and EP4 [73]. Experiments using mice deficient in each of the four PGE₂ receptors established different functions, with EP1 and EP3 having detrimental effects, and EP2 and EP4 being protective [78–83]. PGF₂ α , another major prostaglandin found in brain, appears to have detrimental effects in cerebral ischemia, since prostaglandin F₂ α receptor-deficient mice exhibit less of a neurological defect and smaller infarct volume [84].

The involvement of PGE₂ in AD is controversial. Although PGE₂ was shown to stimulate production of amyloid- β peptides through the EP4 receptor [85], clinical studies did not find reduction in amyloid- β content or in pathology in AD patients treated long term with nonsteroidal anti-inflammatory drugs (NSAIDs) [86,87]. In addition, use of aspirin in AD patients was reported to increase the risk of intracerebral hemorrhage, and heavy use of nonselective NSAIDs in a population study of brain aging and incident dementia showed a higher risk of dementia associated with increased neuritic plaque accumulation [88,89]. A similar picture was provided in reports on ALS. Although deletion of EP2 in the G93A superoxide dismutase model of familial ALS resulted in significant reductions in pro-inflammatory effectors [90], clinical trials using selective COX-2 inhibitors in ALS patients did not show an improvement in morbidity or mortality [91]. More encouraging results were reported in PD patients. Although no protective effect was observed in several trials using aspirin, a 15% reduction in PD incidence was observed in users of nonaspirin NSAIDs [92].

In contrast to neurodegenerative diseases such as ALS, AD and PD, MS is a demyelinating autoimmune disease that involves both innate and adaptive immunity. EAE, a widely used MS model, shares important pathological and mechanistic characteristics with MS, and led to the discovery that Th17 cells play an essential role in autoimmune diseases, including EAE/MS [93,94]. The development of ROR γ t⁺ Th17 cells requires IL-6, IL-1 β and TGF- β , and IL-23 is essential to sustain and expand the Th17 phenotype. PGE₂ has been identified as an inducer of Th17 both indirectly through its effect on DC production of IL-23 [95–98], and directly through effects on CD4⁺ T cells [99,100]. The stimulatory effect of PGE₂ on Th17 differentiation and expansion set up the stage for a possible PGE₂-induced exacerbation in EAE/MS. Indeed, recent lipidomics studies showed preferential presence of PGE₂ and increased EP receptor expression in EAE lesions, and high expression of

mPGES-1 in CNS microglia/macrophages of EAE mice and MS patients [101]. The effect of PGE2 in EAE was directly demonstrated through the *in vivo* use of an EP4-selective antagonist, which decreased the accumulation of Th1 and Th17 and suppressed disease progression [100]. Interestingly, recent studies showed that PGE2 plays a dual role in EAE (i.e., a proinflammatory effect on Th1 and Th17 differentiation during the immunization phase mediated through both EP2 and EP4) and an anti-inflammatory effect in the elicitation phase, mediated through EP4 receptors on brain endothelial cells, and resulting in the protection of the BBB [102]. This exemplifies the multiple PGE2 effects on various cell types and illustrates the difficulty in identifying the precise mechanisms involved in the *in vivo* effects of PGE2.

DHA & its bioactive derivatives

Brain phospholipids are unique in their abundance in the essential n-3 PUFA DHA. Following dietary intake, unesterified DHA and EPA fully cross the BBB through passive diffusion, or as lipoproteins, they are taken up into the CNS in a receptor-mediated manner [103,104]. DHA is preferentially retained in the CNS through mechanisms not yet clarified.

In the neural intracellular compartment, most of the unesterified DHA is processed by acyl-CoA synthetase into 2-lysophospholipids and incorporated into the plasma membrane. Similar to AA, DHA is released by PLA2 enzymes. iPLA2, a group VI calcium-independent PLA2 was proposed to act as a DHA-selective phospholipase [105]. Following intracellular release, DHA can be re-esterified into membrane phospholipids or metabolized through both enzymatic and nonenzymatic pathways. Lipidomics analysis identified several biologically active DHA derivatives (i.e., docosanoids). These include resolvins of the D series (RvD1–4), NPD1, maresins (MaR1) [60,65,106], the cyclopentenone neuroprostanes (A₄/J₄-NPs) [62], and the recently described electrophilic oxo-derivatives (EFOX) (Figure 2) [107]. With the exception of NPD1, the biological effects of DHA derivatives in neuroinflammation have been poorly studied. In experimental ischemia-reperfusion, both NPD1 and aspirin-triggered docosanoids or 17-R resolvins resulting most probably from the activity of acetylated COX-2, were identified in lipidomics studies [108]. In the same study, chronic intracerebroventricular infusion of NPD1 reduced leukocyte infiltration and inflammatory markers more efficiently than DHA, suggesting that the beneficial effect of DHA was mediated through the generation of the bioactive NPD1 [108]. In contrast to NPD1, the function of 17-R resolvins in ischemic injury remains to be determined. In a model of oxygen-induced retinopathy, intraperitoneal administration of RvE1, RvD1 and NPD1 reduced retinal damage to the same level as an n-3 PUFA-enriched diet [109], suggesting again that EPA and DHA derivatives mediate, at least partially, the beneficial effect of n-3 fatty acids. A recent observation, reporting that esterified cyclopentenone A₄/J₄ NP levels are higher in the brain of AD patients, suggests that n-3 fatty acid derivatives can reach biologically relevant concentrations in pathological conditions [62]. However, at this point, it is not possible to compare the efficacy of DHA with its bioactive derivatives due to the lack of information regarding the effects of most of the DHA derivatives in various experimental models of neuroinflammation. Therefore, the rest of this section will deal primarily with the effects of DHA and NPD1.

In agreement with its selective concentration in neuronal, synaptic and retinal membranes, DHA has been shown to play an essential role in prenatal brain and retinal development and to be an important contributor to postnatal homeostatic visual and cognitive functions, and in the control of neuroinflammation [52,58,110]. Impaired postnatal visual and neurological development, as well as macular degeneration and decline in cognitive functions are associated with DHA deficiencies. Several recent publications reported on the effects of DHA and NPD1 in models of neurodegenerative diseases and CNS injury. Dietary DHA was reported to reduce amyloid burden in aged AD transgenic mouse models [111], and its

beneficial effect on synaptic integrity and cognition in AD models has been reviewed recently [112]. It is possible that the beneficial effect of DHA is mediated through NPD1, since treatment of human brain cells with NPD1 resulted in decreased expression of proinflammatory genes known to be upregulated in AD, such as IL-1 β , TNF- α and Cox2. In addition, hippocampal DHA and NPD1 are reduced in AD patients compared with age-matched controls [113]. The involvement of NPD1 is also supported by the fact that both DHA and NPD1 promote the expression of anti-apoptotic Bcl-2 family genes and reduce the expression of pro-apoptotic genes in human brain cells [113].

Dietary DHA proved beneficial in a traumatic brain injury model where 30 days supplementation with dietary DHA resulted in a significant reduction in the number of axons positive for amyloid precursor protein, a marker for axonal injury [114]. A similar conclusion was reached in a spinal cord injury model where daily oral fenretinide for 28 days starting 1 and 6 h after injury resulted in a substantial increase in spinal cord DHA, reduced tissue damage and improved locomotor recovery [115].

We reported that dietary DHA was protective in EAE and that the protective effect was associated with reduced numbers of infiltrating IFN- γ -producing Th1 and IL-17-producing Th17 cells in the spinal cord and brain [116].

Several studies also reported beneficial effects of acute DHA administration. In a spinal cord injury model in rats, DHA intravenous administration attenuated both loss of function and tissue damage [117,118]. Following subcutaneous administration in rats, DHA increased resistance to pentylenetetrazol-induced seizures [119]. In the MCAO model of ischemic stroke, intravenous administration of DHA-albumin and intra cerebroventricular inoculation of DHA or NPD1 reduced infarct volume, neurological deficit and leukocyte infiltration and inhibited NF- κ B binding and Cox2 expression [108,120].

The various cell types affected by DHA and the increasing number of DHA derivatives makes the identification of specific signaling pathways quite difficult. To illustrate the complexity, this is a problem similar to the identification of the signals used by AA without the knowledge of its derivatives and their receptors. The existing information points to several possible DHA targets. The anti-apoptotic effect, especially in neuronal cells, appears to be associated with the activation of the Akt pathway and the induction of anti-apoptotic molecules. DHA promotes the translocation of Akt from the plasma membrane to the cytosol where it is activated and phosphorylated [121]. DHA has also been reported to suppress the inflammatory response in microglia *in vitro* and most importantly *in vivo* following dietary intake [122–124]. In terms of effects on immune cells, DHA is primarily an anti-inflammatory agent. The reduction in proinflammatory cytokine/chemokine expression in cells of the innate immune response could result from the effect of DHA or of its derivatives on different targets. Since DHA is an essential component of the cell membrane, it could interfere with the distribution or function of TLRs. DeSmedt-Peyrusse and colleagues reported that in microglia, DHA impairs the surface presentation of TLR4 but not membrane subdomain localization, and that DHA does not localize in the lipid rafts [122]. We observed that, in DCs, DHA affects signaling through both plasma membrane and endosome-associated TLRs, and that the level of TLR4 surface expression is not affected [125]. In RAW 264.7 cells, DHA inhibited signaling through a constitutively active TLR4, but not through a constitutively active MyD88, suggesting that the effect is upstream of MyD88, presumably at the level of TLR4–MyD88 association [126]. However, in DCs, we observed effects on I κ B and not on NF- κ B p65 phosphorylation, indicative of a DHA effect downstream of MyD88 [125]. These differences are most probably due to various DHA derivatives generated in different cell types and in different experimental conditions.

Docosahexaenoic acid has been reported to function as a peroxisome proliferator-activated receptor (PPAR) γ ligand [127,128]. We and others reported that the inhibition of IL12p70 in DCs treated with DHA was partially mediated through PPAR γ activation [125,129]. The model for ligand-dependent PPAR γ transrepression of cytokine/chemokine genes includes ligand-dependent SUMOylation of PPAR γ followed by binding and stabilization of corepressor complexes. This results in the maintenance of an active suppression of inflammatory genes [130]. Among the DHA derivatives, the electrophilic oxo (EFOX)-derivatives 17-EFOX-D5 and D6 were reported to activate PPAR γ in addition to Nrf2 activation [107].

Recent reports identified Nrf-2 as a transcription factor activated by DHA and the EFOX derivatives [107,131]. Nrf-2 acts as a positive transcription factor for anti-oxidant genes such as hemeoxygenase. Nrf-2 appears to also be involved in the inhibition of proinflammatory genes by DHA, since the inhibitory effect was partially reversed in cells from Nrf-2-deficient mice [131].

Finally, we reported that DHA inhibits NF- κ B nuclear translocation by stabilizing I κ B in a PPAR γ -independent manner [125]. Interestingly, cyclopentenone neuroprostanes have been reported to inhibit IKK resulting in I κ B α stabilization and inhibition of NF- κ B nuclear translocation, without activating PPAR γ [62]. This suggests that various DHA metabolites could initiate different signaling pathways, such as inhibition of NF- κ B or activation of PPAR γ , with the various signals converging on common targets such as the proinflammatory genes.

DCs & lipid mediators

Presently there is no information on the effects of lipid mediators on brain DCs. Therefore, this section will review the existing information on PGE2 and DHA effects on peripheral DCs, and extrapolate the relevant knowledge to neuroinflammation.

PGE2 effects on DC cytokine production, migration & T-cell differentiation

Prostaglandin E2, one of the most abundant AA derivatives produced in physiological and pathological conditions, has been at the center of one of the most intriguing controversies regarding its pro- or anti-inflammatory role. Although some studies indicated that PGE2 contributes to *in vitro* DC maturation in a cytokine milieu [132,133], traditionally, PGE2 has been considered an anti-inflammatory agent based on numerous *in vitro* studies, which reported inhibitory effects on proinflammatory cytokines and upregulation of IL-10 in TLR-stimulated macrophages and DCs, and inhibition of Th1 differentiation [3,134]. However, anti-inflammatory effects of PGE2 were very rarely seen *in vivo*.

Recently, the pro- and anti-inflammatory role of PGE2 has been revisited. Several reports indicate that PGE2 has a stimulatory effect on IL-23 production and on Th17 differentiation. We showed that bone marrow-derived DCs produce higher levels of IL-23 if exposed to PGE2 [97], and that PGE2 exacerbates both trinitrobenzene sulfonic acid-induced colitis and collagen-induced arthritis through the IL-23-IL-17 axis [96,98]. The effects of PGE2 on IL-23 and subsequently on Th17 differentiation were recently confirmed in a number of *in vitro* and *in vivo* studies. Schirmer and colleagues reported that PGE2 released by human fibro-blasts stimulated IL-23 production in DCs and subsequent expansion of Th17 cells, and Myer *et al.* showed increased production of PGE2 in aged DCs leading to significantly higher levels of IL-23 [135,136]. *In vivo* experiments using the EAE model showed suppression of clinical symptoms upon administration of an EP4 antagonist, which correlated with the *in vitro* amplification of IL-23-mediated expansion of Th17 cells [100]. Similar results were obtained in human cells, where PGE2 was found to synergize with

cytokines in promoting Th17 differentiation [99,137]. A recent elegant study by Esaki and colleagues emphasized the complexity of the *in vivo* PGE2 effects. Using the EAE model and various regimens for treatment with EP antagonists, they showed that PGE2 has a dual effect, exacerbating disease in the immunization phase by promoting the generation of Th1 and Th17 cells, and a protective effect on the BBB during the elicitation phase leading to the attenuation of immune cell infiltration into the CNS [102].

Migration of DCs to lymph nodes is an absolute requirement for the activation of naive T cells. It has been known that DC migration requires the expression of CCR7, which allows DCs to respond to the chemokines CCL-19 and -21, constitutively produced in lymph nodes. Although CCR7 is induced following DC maturation, its expression although necessary, is not sufficient for DC migration. PGE2 has been shown to be involved in DC migration *in vitro* as well as *in vivo*, since mice treated with EP4 antagonists or deficient in EP4 exhibit reduced DC migration [138,139]. Although PGE2 does not affect CCR7 expression, it has been reported to participate in the rapid dissolution of podosomes, specialized adhesion structures found in immature DCs [140]. In addition, we showed recently that PGE2 upregulated MMP-9 expression and induced both secreted and membrane-bound MMP-9 in DCs. PGE2-induced MMP9 was essential for DC chemotaxis and matrigel migration in response to CCL19, and for *in vivo* DC migration in both wild-type and MMP-9-deficient hosts [141]. PGE2-induced MMP-9 expression in bone marrow-derived DCs is mediated through the EP4/cAMP/Erk/AP-1 signaling pathway [Yen J-H, Kocieda V, Jung H, Ganea A D, Unpublished Data].

Taken together, these reports strongly support a proinflammatory role for PGE2. PGE2 stimulates mature DC migration to lymph nodes and participates directly and indirectly to the differentiation and maintenance of the Th17 phenotype, a major contributor to autoimmune/inflammatory conditions. In addition, although PGE2 reduces the expression of TNF- α , IL-6, and CCL-3 and -4 in fully differentiated DCs, it has the opposite effect during DC differentiation. Myeloid DCs differentiated from bone marrow cells in the presence of PGE2 secrete higher levels of TNF- α , IL-6 and IL-23 following lipopolysaccharide stimulation, and are better *in vitro* and *in vivo* inducers of Th17 differentiation than their counterparts generated in the absence of PGE2 [95].

DHA effects on DC cytokine production, migration & T-cell differentiation

The molecular/cellular events occurring during exposure of immune cells to DHA or DHA derivatives are poorly understood at present. Although in models of peritonitis, eicosapentaenoic acid and DHA derivatives were shown to reduce neutrophil influx and stimulate macrophage ingestion of apoptotic neutrophils [59], there is little information on their effects on DC and T-cell functions.

Docosahexaenoic acid treatment of human monocyte-derived and of murine bone marrow-derived DCs results in reduced expression of costimulatory molecules and reduced cytokine production [125,129,142,143]. DHA-treated DCs maintained an immature phenotype characterized by high endocytic capacity, high CCR5 expression, chemotaxis in response to CCL3 but not CCL19, and lack of IL-12p70 and IL-23 production following stimulation through both membrane and endosomal TLRs [125]. DHA was reported to inhibit T-cell proliferation directly and indirectly through DHA-treated DCs [116,144]. Also, a previous report showed that DHA-generated NPD1 promoted human T-cell apoptosis by lipid raft clustering [145].

Docosahexaenoic acid-treated DCs were poor stimulators for naive T cells both in terms of proliferation and Th1/Th17 differentiation. This was associated with an increase in p27(kip1) and arrest of T cells in G₀/G₁ [116]. However, the effect of DHA-treated DCs was

limited to naive T cells, and did not result in anergy or development of functional regulatory T cells [116]. The emerging picture is of DHA preventing DC maturation and subsequent naive T-cell stimulation, without affecting effector and possibly memory T cells. DHA does not appear to induce T-cell anergy or regulatory T cells, and therefore seems to function more as a temporary brake than a long-term, antigen-specific suppressor.

Conclusion & future perspective

In the last decade, the nature and function of lipid mediators in various biological setups received a lot of attention and scrutiny, leading to a large amount of new data and to many interpretations, some of them contradictory. n-6 and n-3 PUFAs have been at the forefront of lipid biological research. In this article we reviewed the existing information on the function of the major AA-derived metabolite PGE₂, and of DHA, the major CNS n-3 PUFA, in specific aspects of neuroinflammation. We focused on the effects of PGE₂ and DHA on DCs, whose role in CNS autoimmune diseases, CNS injury including cerebral ischemia, and neurodegenerative diseases, has received special attention in the last few years. In EAE, perivascular DCs are recruited from the periphery whereas parenchymal DCs, whose origin is not entirely clear, could originate in the periphery or differentiate from resident microglia. Perivascular myeloid DCs have been shown to play an essential role in the reactivation of encephalitogenic T cells. In cerebral ischemia and other types of CNS injury, DCs are among the first peripheral immune cells to infiltrate the injured area. Both activated microglia and DCs can secrete a variety of cytokines and chemokines, activate CD4⁺ T cells and affect T-cell differentiation. Recently, αβTh17 and γδT17 cells have been shown to be major pathogenic agents in EAE and cerebral ischemia/reperfusion models. Amplification of Th17 cells and induction of IL-17 in γδ T cells depends on IL-23, a cytokine produced by activated DCs and microglia. Although there is no direct information on the effects of lipid mediators on CNS DCs, a picture of divergent effects of PGE₂ and DHA emerged recently from studies done with peripheral DCs. The most important differences from the point of view of this article are the effects on MMP-9 and IL-23. PGE₂ promotes, whereas DHA prevents DC maturation. PGE₂ promotes DC MMP-9 and IL-23 expression, whereas DHA inhibits both. In terms of the DC activation of T cells, PGE₂ promotes DC-induced T-cell proliferation and differentiation into Th17, whereas DHA inhibits both. In addition, DHA also has an inhibitory effect on Th1 differentiation. Therefore, depending on the prevalence of PGE₂, and possibly of other proinflammatory prostanoids, or of DHA and possibly of DHA metabolites such as NPD1, EFOX and neuroprostanes, perivascular or parenchymal DCs could act either as pro- or anti-inflammatory agents. As a result, the development and function of Th1, Th17 and γδT17 cells could be amplified or inhibited (Figure 3). In addition, MMP-9 expression, which is promoted by PGE₂ and inhibited by DHA, could play an important role in DC migration to and within the CNS. Although this is an oversimplified picture of the actions of n-6- and n-3-derived lipid mediators in the CNS, we hope that it represents a framework for future studies on their effects on DCs, microglia and infiltrating T cells in various neuroinflammatory models.

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Executive summary

CNS dendritic cells

■ In contrast to most tissues, brain dendritic cells (DCs) are rarely detected in healthy brain parenchyma, where they appear to be involved in neurogenesis. In contrast, the number of DCs increases significantly in neuroinflammation associated with CNS trauma, autoimmunity and infectious processes. DCs play an important role in neuroinflammation both as participants in innate proinflammatory responses and through effects on T-cell activation and differentiation.

Role of n-6 fatty acid (arachidonic acid derivatives) in central neuroinflammation

■ Most of the existing information points to PGE₂ as an important activating factor in neuroinflammation, particularly in experimental autoimmune encephalomyelitis/multiple sclerosis where stimulation of IL-23 production in DC and microglia results in sustained activation of IL-17-producing T cells.

Role of n-3 fatty acids (docosahexaenoic acid & its derivatives) in central neuroinflammation

■ Docosahexaenoic acid plays a beneficial role in CNS trauma and neurodegenerative diseases through effects on Toll-like receptors, peroxisome proliferator-activated receptor- γ activation, inhibition of NF- κ B translocation and activation of the transcription factor Nrf2.

Dendritic cells & lipid mediators

■ Prostaglandin E₂ affects DC function in terms of cytokine production and migration, by stimulating the production of IL-23 and the expression of CCR7 and matrix metalloproteinase 9, and promotes Th17 differentiation/function.

■ By contrast, docosahexaenoic acid inhibits DC-derived cytokine production, including IL-23, and prevents Th17 differentiation/function.

Figure 1. Effects of arachidonic acid metabolites

Free AA released from membrane phospholipid stores by PLA2 is processed by COX and LOX enzymes into PGs, thromboxanes, LTs and LXs. Most PGs and LTs promote inflammation, whereas LXs are anti-inflammatory.

AA: Arachidonic acid; COX: Cyclo-oxygenases; LOX: Lipo-oxygenases; LT: Leukotriene; LX: Lipoxin; PG: Prostaglandin; PLA2: Phospholipase A2.

Figure 2. Effects of docosahexaenoic acid metabolites

Free DHA released from membrane phospholipid stores by PLA2 undergoes enzymatic and nonenzymatic conversions to various metabolites. Nonenzymatic peroxidation results in the generation of the electrophilic cyclopentenone neuroprostanes A4 and J4, which inhibit NFκB activation. Conversion of DHA into NPD1 by 15-lipo-oxygenase enzymes leads to inhibition of NFκB, COX-2 and of proapoptotic Bcl-2 family proteins, while promoting the expression of anti-apoptotic Bcl-2 proteins. COX-2 and aspirin-treated COX-2 catalyze the formation of EPOX-derivatives D5/D6, which activate PPAR-γ and Nrf2, a transcriptional activator of antioxidant genes. In addition, DHA also acts as a PPAR-γ ligand and prevents the association of TLR 4 with MyD88, interrupting TLR signaling in immune cells.

DHA: Docosahexaenoic acid; EPOX: Electrophilic oxo-derivatives; NPD1: Neuroprotectin 1; PPAR: Peroxisome proliferator-activated receptor; TLR: Toll-like receptor.

Figure 3. Differential effects of prostaglandin E2 and docosahexaenoic acid on dendritic cell maturation leads to opposite experimental autoimmune encephalomyelitis severity

Peripheral DCs undergo maturation in response to TLR stimulation and/or proinflammatory cytokine signaling. DC maturation is associated with increased MHCII and costimulatory molecule (CD40, CD80 and CD86) expression, proinflammatory cytokine production and upregulation of MMP-9 and CCR7. PGE2 promotes DC maturation, increasing IL-1 β , -6 and -23, and CCR7 and MMP-9 expression. By contrast, DHA prevents MHCII and costimulatory molecule upregulation, inhibits IL-1 β , -6 and -23, and prevents CCR7 and MMP-9 expression. Both PGE2 and DHA inhibit IL-12 production and therefore reduce Th1 differentiation. However, PGE2 and DHA exert opposite effects on Th17 differentiation through their effects on IL-6, -1 β and especially IL-23. In addition, activation of IL-17 production in $\gamma\delta$ T cells, which occurs in the presence of IL-1 β and -23, is also inhibited by DHA. Following the opposite effects on CCR7 and MMP-9, PGE2 promotes, and DHA prevents migration of DCs to lymph nodes and the CNS. The final outcome is that exposure of DCs to DHA results in a decrease in Th1, Th17, proinflammatory cytokines and CNS migration of DCs, leading to a reduction in neuroinflammation and EAE severity. By contrast, exposure of DCs to PGE2 results in an increase in Th17 and DC migration, as well as increased proinflammatory cytokines, exacerbating neuroinflammation.

BBB: Blood–brain barrier; DC: Dendritic cell; DHA: Docosahexaenoic acid; EAE: Experimental autoimmune encephalomyelitis; MMP: Matrix metalloproteinase; PG: Prostaglandin; TLR: Toll-like receptor.