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Review

Alterations of brain eicosanoid synthetic pathway in multiple sclerosis and in animal models of demyelination: Role of cyclooxygenase-2

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ABSTRACT

Inflammation is a physiological response to exogenous and endogenous stimuli and, together with demyelination and immune system activation, is one of the key features of multiple sclerosis (MS). Arachidonic acid (AA) metabolism by cyclooxygenase (COX) and lipoxygenase (LO) enzymes leads to the production of proinflammatory eicosanoids, and stimulates cytokine production and activation of microglia and astrocytes, thereby contributing to MS pathology. Current therapies target the immune system but do not specifically target AA-related inflammatory pathway. Corticosteroids and non-steroidal anti-inflammatory drugs (NSAIDs) are frequently associated with immunomodulatory therapies to treat flu-like adverse effects. Few clinical and mounting preclinical data in MS show that AA metabolism contributes to immune system activation, demyelination and motor disabilities, and administration of NSAIDs reduces these symptoms. The beneficial effect of NSAIDs seems to be a prerogative of COX-2 selective inhibitors and suggests that NSAIDs selective for COX-2 may be more effective than mixed COX-1/2 inhibitors.

1. Pathophysiology of multiple sclerosis

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system (CNS) with uncertain etiology, affecting about 2.1 million people worldwide in their early adulthood. Genetic, environmental and immunological factors may all be at play [1]. Patients affected by MS develop motor and cognitive dysfunction including deficits in memory, learning, attention and information processing [2].

At the molecular level, the hallmarks of MS pathology are brain demyelination and inflammation. Demyelination is a degenerative process associated with mature oligodendrocyte death, myelin loss, and formation of demyelinating plaques (commonly known as "scars"). Inflammation is characterized by activation and proliferation of astrocytes, microglia/macrophages and lymphocytes (mostly $CD8^+$ T cells) infiltration to the site of demyelination, activation of the inflammatory pathway of arachidonic acid (AA) and production of proinflammatory mediators such as chemokines and cytokines [3]. Demyelinating lesions have been classified into four patterns based on plaque morphology, myelin protein expression, oligodendrocyte pathology and presence of complex deposition [4]. In patterns I and II, demyelination is secondary to an auto-immune reaction against myelin, whereas in patterns III and IV demyelination is independent by an immune activation and is caused by oligodendrocyte primary damage and degeneration [4]. Specifically, pattern I manifests with T cells and macrophages infiltration, whereas pattern II presents Ig deposition and products of complement activation. Pattern III lesions show pronounced oligodendrocyte apoptosis associated with loss of myelin basic protein (MBP) and 2′, 3′-cyclic nucleotide 3′-phosphodiesterase (CNPase), production of oxygen radicals and mitochondrial dysfunction. Finally, pattern IV lesions show oligodendrocyte degeneration in the white matter surrounding the active lesion. It has been hypothesized that demyelination is secondary to immune system activation as a consequence of T-cells infiltration into the brain. However, the more recent new classification of MS indicates that patterns III and IV of MS lack of immune system activation, suggesting that mechanisms other than the immune hypothesis are implicated in oligodendrocyte death.

Available treatments for MS reduce symptoms and severity of the disease, but no cure is available. First line disease-modifying FDA-approved drugs, such as interferon (IFN)-1β and -1α, glatiramer acetate, natalizumab, fingolimod and mitoxantrone, are mostly immunomodulatory. Immunomodulatory drugs act by inhibiting the lymphocyte recall to CNS and the immune system activation, and are usually associated with a wide range of severe side effects and modest efficacy [5,6]. MS patients are frequently treated with anti-inflammatory drugs such as corticosteroids and non-steroidal drugs (NSAIDs) to control flu-like symptoms associated to first-line therapy, but whether they also have a

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therapeutic effect remains to be clarified. Here we summarize clinical evidences of altered AA metabolism and data on anti-inflammatory therapy in MS patients and preclinical data from experimental models suggesting a potential role for selective NSAIDs in limiting the pathogenesis and progression of MS.

2. Activation of arachidonic acid metabolism in MS

The AA cascade is stimulated during inflammatory conditions and its pathway is inhibited with NSAIDs to reduce inflammation. Activation of AA metabolism has been reported in MS [7–17]; however, due to limited and heterogeneous clinical studies, it is unclear whether AA cascade is involved in the initiation or progression of demyelination. Notably, AA is released from the cell membrane into the cytoplasm in response to proinflammatory stimuli by the activity of phospholipases A_2 (PLA_2) and then metabolized by cyclooxygenase (COX)-1 and -2 enzymes to bioactive pro-inflammatory prostaglandins (PGs), and by lipoxygenases (LOs) to pro-inflammatory leukotrienes (LTs) and anti-inflammatory lipoxins (LXs).

Levels of COX-derived PGI_2, $PGF_{2\alpha}$, PGD_2 and particularly PGE_2, have been found increased in the cerebrospinal fluid (CSF) of MS patients during both relapsing and remitting phases, but their function remains unclear [10–12]. Supporting a role during the remission phase, a comparison between PGs level in the CSF during relapse and remission phases shows that PGE_2 and $PGF_{2\alpha}$ concentrations were higher during remission [13]. Conversely, supporting a role in the pathogenesis and progression, Dore-Duffy et al. in 1986 showed increased baseline levels of PGE_2 in leukocyte cultures from patients who had at least one recent exacerbation or chronic progressive or stable MS compared to healthy controls [9]. Patients with active symptoms also exhibited a sharp increase in PGE_2 release early in or just before the onset of clinical symptoms [9].

Among PGs, the increase in the level of PGE_2 seems to be the most remarkable and suggests a possible role in demyelination. However, Mattsson et al. reported a lack of correlation between the increase in the level of PGE_2 and the clinical scores of MS severity as indicated by the measurement of biochemical markers of axonal and astroglial injury [14].

Interestingly, the protein expression of the AA metabolizing enzyme COX-2 was increased in regions of active demyelination in MS post-mortem brain. COX-2 was co-expressed mostly with markers of macrophages/microglia [15] and dying oligodendrocytes in the white matter of MS patients, as shown by triple immunofluorescence using antibodies against COX-2, the myelin marker CNPase and activated caspase-3 as a marker of apoptosis [16,17]. Furthermore, genetic variants in the *ptgs2* gene, which codes for COX-2, have been identified as modulators of the response to COX-2-inhibiting drugs and possible risk factors for the incidence or prognosis of MS [18]. Increased expression of COX-2 in demyelinating lesions and in dying oligodendrocytes, and increased PGs levels in the CSF of MS patients suggest that this pathway is involved in the disease genesis and progression; animal studies in various models of demyelination support this concept [9–13,15–17].

As mentioned earlier, AA is also metabolized by LOs. Increased expression of 5-LO in demyelinating lesions [19,20] and increased levels of its LT products in the CSF [7] were reported in MS patients [10,14]. Furthermore, the 15-LO derived 15-HETE was increased in the CSF of patients as well [14]. However, Mattson et al. did not find any correlation between 15-HETE levels and the degree of disability grade in MS [14].

Other AA products have been measured in MS patients including isoprostanes, which are free radicals produced *via* a lipid peroxidation reaction independently by COXs and LOs activity, like the 8-epi $PGF_{2\alpha}$ which was three-fold up regulated in MS patients and correlated with the disability grade [11].

3. Effect of NSAIDs in MS

NSAIDs, inhibitors of COX-1 and -2, are commonly given to MS patients to attenuate flu-like symptoms associated with immunosuppressive drugs such as IFN-β [6]. Several studies showed that the non-selective COX-inhibitors ibuprofen and indomethacin, and the selective COX-2 inhibitor acetaminophen were effective in reducing IFN-β induced flu-like symptoms [21–25]. Another study using either naproxen (non-selective), ibuprofen or acetaminophen reported that, although IFN-β side effects were not reduced, patients treated with naproxen and ibuprofen experienced an improvement of the Modified Fatigue Impact Scale (MFIS) for physical subset, while acetaminophen-treated patients showed increased MFIS for improved cognitive subset [26]. Fatigue severity was ameliorated in another small-randomized double-blind study of thirty patients treated with aspirin (1300 mg/day) [27]. However, none of the trials evaluated specific COX-related beneficial effects on demyelination, neuroinflammation or clinical course of the disease.

4. Animal models of MS

Because of the heterogeneity and unclear etiology of MS, several animal models have been developed. The most commonly used rodent model of MS is the experimental autoimmune encephalomyelitis (EAE), where the pathology is induced by immunization against a myelin-specific antigen in the spinal cord. Other commonly used animal models of demyelination are the cuprizone intoxication model, which causes severe brain demyelination and mature oligodendrocyte loss [28], and the Theiler's murine encephalomyelitis virus (TMEV), induced with the picornavirus [29]. Lucchinetti and colleagues [30] suggest that EAE is best poised to investigate mechanisms of immune-mediated lesions such patterns I and II of MS; whereas the cuprizone model is useful to investigate patterns III and IV lesions where demyelination is induced by a functional damage of oligodendrocytes, hypothetically induced by infections or unknown toxins or chemicals [28,30]. On the other hand, the TMEV supports the viral hypothesis of MS [29].

EAE is induced *via* subcutaneous injection of encephalitogenic peptides such as myelin oligodendrocyte glycoprotein (MOG) or proteolipid protein (PLP) emulsified in complete Freund's adjuvant containing mineral oil and *Mycobacterium tuberculosis*, followed by intraperitoneal injection of pertussis toxin. A different phenotype of EAE is induced *via* intravenous injection of myelin-reactive $CD4^+$ Th1 lymphocytes [31]. The EAE model shares similarities with the human MS pathology such as demyelination and motor dysfunction. However, the mouse model primarily shows severe spinal cord pathology but mild brain inflammation, neurodegeneration and synaptic loss [32,33]. EAE remains the most extensively used in the scientific scenario, and has been extremely helpful to the discovery of therapies for MS [34].

Cuprizone [oxalic acid bis(cyclohexylidene hydrazide)] is a copper chelator capable of causing selective apoptosis of mature oligodendrocytes, and used as tool to induce brain demyelination. The exact mechanism by which cuprizone leads to a specific and selective oligodendrocyte death is not fully understood. However, since cuprizone interferes with mitochondrial function by inhibiting the copper-dependent mitochondrial enzymes cytocrome oxidase and monoamine oxidase, it can interfere with mechanisms of mitochondria respiration and cause, in turn, oligodendrocyte

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apoptosis, due to high metabolic rate of oligodendrocyets [35]. Supporting this hypothesis, mitochondria enzymes are altered during the first days of cuprizone exposure, prior to demyelination, suggesting a causative role [36]. A cuprizone 0.2% diet (w/w) is fed to mice for 6 weeks to induce demyelination in corpus callosum, cortex and hippocampus with a peak of demyelination occurring between week 5 and 6 [37,38]. Along with demyelination, a massive inflammatory reaction occurs, with microglia/macrophages infiltration and astrocyte proliferation into the demyelinated regions [38]. Moreover, in response to oligodendrocyte loss, mechanisms of remyelination are triggered and lead to oligodendrocyte precursor proliferation and migration from the sub ventricular zone, and a slight increase in myelin content from 5 to 6 weeks of cuprizone exposure [38–40]. Demyelination and neuroinflammation are also accompanied by axonal damage [41], as shown by increased production of the amyloid precursor protein (APP) protein [41], and motor disabilities [42], as seen in MS. The cuprizone model is also useful to study mechanisms involved in the remyelination process because the mouse brain spontaneously and fully remyelinates within 6 weeks upon cuprizone withdrawal from the diet [28].

Epidemiological evidences suggest that viral infections may be associated with the onset of MS pathology [29]. In the TMEV model, mice are injected with an intracerebral injection of neurotropic picornavirus, which causes progressive $CD4^+$ T-cell-mediated demyelination with a strong immune activation against myelin antigens [29]. Together with demyelination, several inflammatory cytokines and chemokines are produced by macrophages and glia [43]. Theiler's virus injection induces a biphasic disease (acute phase and chronic phase) in susceptible mouse strains. One week after infection (acute phase), TMEV causes polioencephalomyelitis, characterized by neuronal apoptosis in the brain gray matter. After 1 month (chronic phase), a reaction of glia and macrophages is visible; demyelination, oligodendrocyte apoptosis and axonal degeneration are detected in the white matter of the spinal cord [44]. Because of these characteristics, the TMEV is a useful model of viral-induced CNS pathology, and is considered to be relevant to chronic/progressive MS [29].

5. Activation of arachidonic acid metabolism in animal models of MS

Among AA-derived prostaglandins, PGE_2 is consistently affected in various animal models of MS similarly to MS patients.

In the EAE model, PGE_2 level was elevated in the spinal cord and correlated with the degree of disability whereas PGI_2 and PGD_2 were decreased [45]. A dual role for PGE_2 in regulating T cells development and blood brain barrier (BBB) permeability in the EAE model was proposed; specifically, PGE_2 facilitates Th1 and Th17 cell generation through its receptors EP4 and EP2, and modulates T-cell infiltration into the brain *via* EP4 [46]. More recently, PGs were measured in the cerebral cortex of cuprizone-intoxicated mice giving a different spectrum of changes. The PGE_2, PGD_2 and TXB_2 were increased in the cortex during demyelination with the change of PGE_2 being the most pronounced, whereas PGI_2 level was not changed [47].

Consistent with human finding, studies in TMEV and in the cuprizone-induced demyelination demonstrated that COX-2 is expressed by mature oligodendrocytes undergoing apoptosis [17,48], suggesting that COX-2 plays a role in mediating oligodendrocyte apoptotic death. Immunohistochemical investigation in the cuprizone model additionally demonstrates that the downstream PGE_2 receptor EP2 is also expressed by oligodendrocytes after one week of cuprizone exposure, when oligodendrocytes undergo caspase-3 mediated apoptosis, preceding histological demyelination [48].

Conversely, the COX-1 isoform does not seem to be directly linked to the pathogenesis of demyelination in animal models of MS. Data from the cuprizone model show that COX-1 gene and protein expression are elevated in the brain during the pick of demyelination; however, the homozygous deletion of COX-1 gene in mice did not prevent or ameliorate any of the MS-like pathology [47].

Little is known about the role of LO-mediated metabolism of AA in MS. One study demonstrated that 5-LO gene and protein expression is increased during processes of demyelination. This activation was linked to axonal damage and motor dysfunction without being implicated in demyelination [49]. Although many 5-LO inhibitors, such as MK0633 and Zileuton, have been tested in clinical trials for the treatment of asthma and other obstructive pulmonary diseases, there are no clinical trials for the treatment of MS patients [50,51].

6. Effect of NSAIDs in animal models of MS

The contribution of COX to the pathogenesis of demyelination has been investigated in animal models of MS. In the EAE model, non-selective COX inhibitors (indomethacin and naproxen) and COX-2 selective inhibitors (rofecoxib, lumiracoxib and celecoxib) showed inhibition of immune system activation, inflammation and demyelination [52–56]. Selective COX-2 inhibitors ameliorated EAE pathology by modulating IFN-β and IL-10 production and inhibiting Th1 immunoresponse and T-cell recruitment into the CNS [55,56]. Interestingly, early administration of celecoxib or of an EP2 receptor antagonist to cuprizone-treated mice dramatically reduced oligodendrocyte apoptosis, demyelination and significantly attenuated motor disability [48].

Although the exact mechanism of COX non-selective and COX-2 selective inhibitors efficacy is not known, one could speculate that they act by inhibition of PGs production, and particularly of PGE_2, being increased both in the EAE and in the cuprizone models [45,57]. PGE_2 acts *via* G protein-coupled EP receptors and the EP2 subtype has been proposed to mediate oligodendrocyte damage [48]. Additional studies are needed to further elucidate the specific involvement of downstream EP receptors in demyelination as well as in myelin repair.

7. Conclusions

Evidence from both clinical data in MS patients and animal models of demyelination supports a role for AA-mediated inflammation in the pathophysiology of MS. Levels of AA-derived proinflammatory PGs, especially PGE_2, are dramatically increased in the cerebrospinal fluid of patients and in the brain and spinal cord of animal models of MS (Table 1). Of the two isoforms responsible for the metabolism of AA, COX-2 seems to play a key role in the demyelinating process. Specifically, COX-2 (but not COX-1) colocalizes with apoptotic oligodendrocytes and the use of COX-2 selective inhibitors was effective in counteracting demyelination, immune system activation and the severity of disabling motor dysfunctions in the cuprizone model (Fig. 1). Literature suggests that the choice COX-2 selective inhibitors rather than mixed COX inhibitors, is more effective in experimental models of MS. Clinical trials suggest that mixed COX inhibitors improved MFIS, and acetaminophen, which selectively inhibits COX-2, improved the cognitive subset. Experimental data encourage further investigation of the effectiveness of selective COX-2 inhibitors in MS.

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Table 1
A comparison between human data from MS patients and experimental preclinical models of MS regarding changes of COX-2 and COX-derived products in the CNS, and evidence of NSAIDs (COXs non-selective inhibitors versus COX-2 selective inhibitors) efficacy in MS. MFIS = Modified Fatigue Impact Scale, and NT = not tested.

Subject	CNS changes of COX-2 and COX-derived products		Evidences of NSAIDs efficacy against MS pathology							
	COX-2 expression	COX-derived products	COX non-selective				COX-2 selective			
			Indomethacin	Naproxene	Ibuprofen	Aspirin	Rofecoxib	Celecoxib	lumiracoxib	Acetaminophen
Human	↑ In active plaques ↑ In apoptotic oligodendrocytes [16,17]	↑PGE_2,↑PGI_2, $PPGD_2$, ↑$PGF_{2\alpha}$ In CSF [9–12]	Reduces IFN-β/flu-like symptoms [22]	Improves MFIS [26]	Reduces IFN-β/flu-like symptoms improves MFIS [23–25]	Improves MS-related fatigue [27]	NT	NT	NT	Reduces IFN-β/flu-like symptoms, improves MFIS [23–25]
Mouse EAE	NT	↑PGE2,↓PGI2,↓PGD2 In spinal cord [45]	Reduces demyelination, immune system activation, inflammation [52]	Reduces demyelination, immune system activation, inflammation [53]	NT	NT	Reduces demyelination, immune system activation, inflammation [55]	Reduces demyelination, immune system activation, inflammation [56]	Reduces demyelination, immune system activation, inflammation [55]	NT
Mouse cuprizone	↑ In apoptotic oligodendrocytes [48]	↑PGE2,= PGI2,↑PGD2, ↑TXB_2 In cortex [47]	NT	NT	NT	NT	NT	Reduces oligodendrocyte, apoptosis, demyelination, motor disfunction [48]	NT	NT
Mouse Theiler's virus	↑ In apoptotic oligodendrocytes [17]	NT	NT	NT	NT	NT	NT	NT	NT	NT

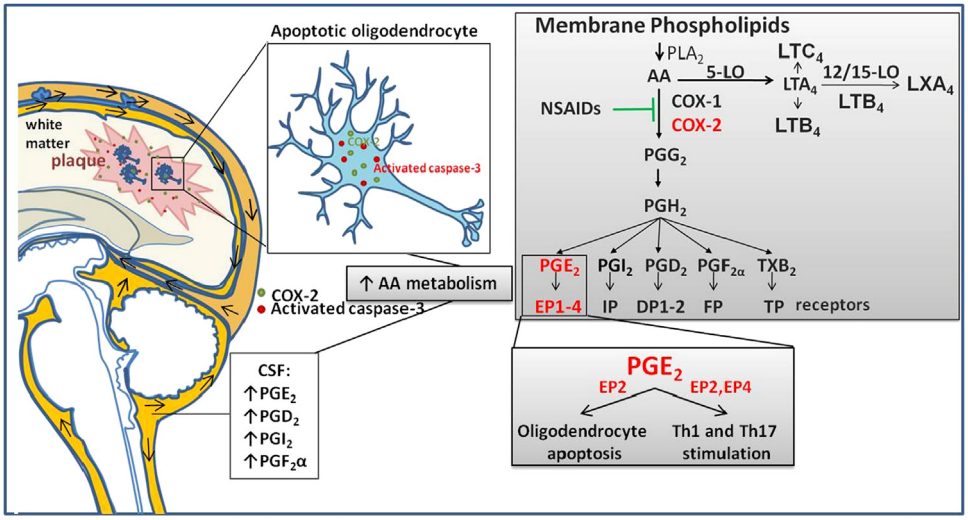

Fig. 1. MS-related changes of COX-2 and COX-derived PGs expression in the human CNS. Arrows in the subarachnoid space and ventricular system of the brain (left) indicate the flow of PGs within the CSF. A list of PGs that have been reported to be altered in MS patients is shown. In the white matter of the brain of MS patients, demyelinating plaques show increased intracellular expression of COX-2 (black dots) and of the pro-apoptotic protein caspase-3 (white dots), mostly in oligodendrocytes (magnification of one representative apoptotic oligodendrocyte on the right side of the brain). AA acid cascade, right side of the image the putative pathway contributing to MS-like pathology (demyelination and immune system activation) is highlighted (COX-2/PGE_2/EP_2/EP_4). AA = arachidonic acid, LO = lipoxygenase, LT = leukotriene, LX = lipoxin, COX = cyclooxygenase, CSF = cerebrospinal fluid, PG = prostaglandin, and TX = thromboxane.

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