7 Pathogenesis and Progression of Multiple Sclerosis: The Role of Arachidonic Acid–Mediated Neuroinflammation

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Doi: http://dx.doi.org/10.15586/codon.multiplesclerosis.2017.ch7

Abstract: Multiple sclerosis is characterized by inflammatory processes occurring within the central nervous system. In multiple sclerosis, inflammation could be either a physiological response secondary to the immune system activation or a phenomenon triggered by primary cytodegeneration of neurons and/or oligodendrocytes without the involvement of immune cells. The arachidonic acid metabolism is activated via cyclooxygenases (COXs) and lipoxygenases (LOXs) in postmortem brain samples and in the cerebrospinal fluid of multiple sclerosis patients. It has been hypothesized that the arachidonic acid–mediated neuroinflammation could play a role in the pathogenic mechanisms triggering demyelination, oligodendrocyte loss, axonal pathology and, ultimately, motor dysfunctions, which are hallmarks of multiple sclerosis. COX-2 and 5-LOX selective inhibitors efficiently inhibit each of the hallmarks mentioned above in different animal models of multiple sclerosis. Thus, it is suggested that the arachidonic acid pathway represents a potential pharmacological target to ameliorate multiple sclerosis pathology and symptoms.

In: *Multiple Sclerosis: Perspectives in Treatment and Pathogenesis*. Ian S. Zagon and Patricia J. McLaughlin (Editors), Codon Publications, Brisbane, Australia. ISBN: 978-0-9944381-3-3; Doi: http://dx.doi.org/10.15586/codon.multiplesclerosis.2017

Key words: Arachidonic acid; Cyclooxygenases; Inflammation; Lipoxygenases; Multiple sclerosis

Introduction

Multiple sclerosis is a multifactorial degenerative disease of the central nervous system characterized by immune system activation, inflammation, and demyelination. The genesis of the inflammatory process and its role in the onset and progression of the disease is still under debate, although advances have been made over the past decades of scientific research. For instance, it has been hypothesized that the central inflammation observed in multiple sclerosis is a physiological response secondary to the immune system activation. Different subtypes of $CD4^+$ T helper lymphocytes—Th1 and Th17—and cytotoxic $CD8^+$ lymphocytes have been shown to trigger neuroinflammation in multiple sclerosis (1). These activated lymphocytes migrate to the brain, recall peripheral monocytes/macrophages, and ultimately lead to myelin loss and apoptosis and/or necrosis of mature oligodendrocytes. Resident astrocytes and microglia are activated after lymphocytes infiltration. As a consequence, several inflammatory mediators like cytokines (chemokines, IL2, IL3, TNFα, IFNγ, and many others) are released by these cells in the extracellular compartment where they exert cytotoxic activity against oligodendrocytes (2–5).

In some types of multiple sclerosis, the disease seems to develop independently of the autoimmune mechanisms, particularity in those disease types—histological patterns III and IV—that show no evidence of immune activation at demyelinated lesions (6, 7). In these cases, inflammation maybe triggered by primary cytodegeneration of neurons and/or oligodendrocytes without the involvement of immune cells (8). Regardless of the biological process underlying inflammation, it has been consistently shown that inflammation is directly involved in the progression of multiple sclerosis (9). In recent years, there has been a growing interest in understanding the role of inflammatory mediators derived from the activation of arachidonic acid metabolism (e.g., prostaglandins and leukotrienes) in the disease (10). Prostaglandins and leukotrienes are abundantly produced in the central nervous system of multiple sclerosis patients, contributing to the severity of the disease. Therefore, it has been suggested that anti-inflammatory treatments targeting the arachidonic acid pathway, by using nonsteroidal anti-inflammatory drugs (NSAIDs), might be beneficial for treating multiple sclerosis.

Activation of the Arachidonic Acid Cascade in Multiple Sclerosis

Scientific evidences show that arachidonic acid metabolism is excessively activated in the central nervous system of multiple sclerosis patients as well as in the brain of animals from experimental models of multiple sclerosis. It has been hypothesized that arachidonic acid products could play a role in the pathogenic mechanisms underlying demyelination, oligodendrocytes loss, and axonal pathology that represent common hallmarks of multiple sclerosis. Arachidonic acid is a

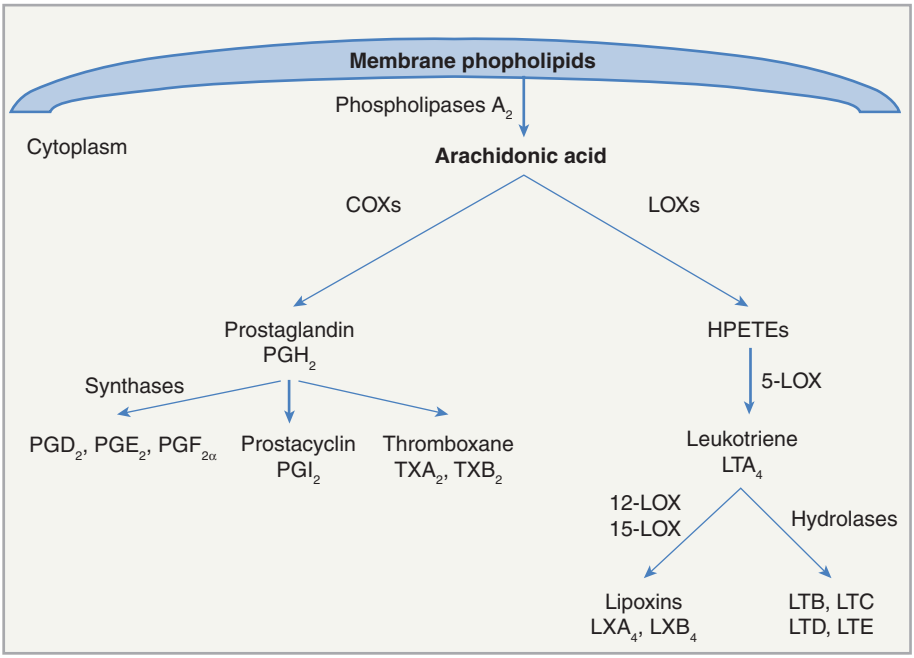

Figure 1 **Schematic representation of the arachidonic acid metabolic pathway.**
COX= cyclooxygenase, LOX= lipoxygenase, HPETE= hydroperoxyeicosatetraenoic acid.

membrane omega-6 fatty acid molecule released in the cytoplasm by the hydrolytic activity of the cytosolic phospholipase A_2 ($cPLA_2$) (Figure 1). It has been shown that the concentration of several molecules that activate $cPLA_2$, such as reactive oxygen species and cytokines, is increased in multiple sclerosis (11–14). After being released into the cytoplasm, arachidonic acid is metabolized by the activity of cyclooxygenases (COXs) 1 and 2 into prostacyclins, prostaglandins (PGs), and thromboxanes (TXs), and by the lipoxygenases (LOXs), 5-LOX, 12-LOX and/or 15-LOX into leukotrienes (LTs) and lipoxins (LXs). As far as COXs are concerned, both isoforms lead to the production of PGE_2. COX-1 is constitutively expressed, whereas COX-2 is induced during inflammation and seems to be the major source of PGE_2 production. Particularly, COX-2 expression appears to be induced in oligodendrocytes and immune cells during the processes of demyelination (15–17). The proinflammatory PGs and LTs that are upregulated in multiple sclerosis represent promising therapeutic targets as suggested by animal models of multiple sclerosis.

ARACHIDONIC ACID PATHWAY ACTIVATION IN PATIENTS AFFECTED BY MULTIPLE SCLEROSIS

Arachidonic acid activation has been found in the cerebrospinal fluid and in postmortem brain of multiple sclerosis patients (see Table 1 for details of primary data). It has been shown that COX-2 is expressed in active demyelinating lesions (15), and also in dying oligodendrocytes (16) suggesting a potential role for

TABLE 1 **Primary data concerning arachidonic acid pathway alterations in the CSF, brain tissue, and peripheral blood of multiple sclerosis patients and in the brain of EAE, TMEV, and cuprizone mice**

		Multiple Sclerosis Patients	*Animal Models of Multiple Sclerosis*		
			EAE model	TMEV model	Cuprizone model
Cyclooxygenase (COX) pathway	COX-1	NT	4-fold increase of mRNA (27); expressed in microglia/ macrophages (29)	NT	Up to 30% increase in protein, 70% increase in mRNA (34); expressed in microglia and/or macrophages and astrocytes
	COX-2	Expressed in brain tissue within apoptotic oligodendrocytes and microglia and/or macrophages (15–17)	Up to 5-fold increase of mRNA (27,31); expressed in microglia and/or macrophages and in endothelial cells (28–29)	Expressed in apoptotic oligodendrocytes and in astrocytes (15–16)	No change in protein, 50% increase in mRNA (34); expressed in apoptotic oligodendrocytes (34, 35)
	PGD_2	Expressed in the CSF of patients only (18)	No change—50% decreased levels (27,31)	NT	Up to 1-fold increased levels (34, 35)
	PGE_2	Increased levels in the CSF (18–20) and in peripheral lymphocytes (21)	1-fold increased levels (27,31)	NT	Up to 5-fold increased levels (34, 35)
	$PGF_2\alpha$	Increased levels in the CSF (18–20)	No change (27)	NT	NT
	PGI_2	Increased levels in the CSF (18)	2-fold increased levels (27)	NT	50% increased levels (34)
	TXA_2	NT	NT	NT	NT
	TXB_2	NT	50% decreased levels (27)	NT	Up to 1-fold increased levels (34, 35)

Table continued on following page

TABLE 1 **Primary data concerning arachidonic acid pathway alterations in the CSF, brain tissue, and peripheral blood of multiple sclerosis patients and in the brain of EAE, TMEV, and cuprizone mice** (Continued)

		Multiple Sclerosis Patients	*Animal Models of Multiple Sclerosis*		
			EAE model	TMEV model	Cuprizone model
Lipoxygenase (LOX) pathway	5-LOX	NT	8-fold increase of mRNA (27)	NT	30% increase of protein, 3.5-fold increase of mRNA (39)
	12-LOX	NT	10-fold increase of mRNA (27)	NT	NT
	15-LOX	NT	10-fold increase of mRNA (27)	NT	NT
	LTB_4	40–100% increase in the CSF (22, 23)	50% decrease (27)	NT	NT
	LTC_4	0–30% increase in the CSF (18, 22, 23)	80% decrease (27)	NT	NT
	LTD_4	No change in the CSF (23)	60% decrease (27)	NT	NT
	LTE_4	No change in the CSF (23)	NT	NT	NT
	LXA_4	NT	NT	NT	NT
	LXB4	NT	NT	NT	NT

NT= not tested, CSF= cerebrospinal fluid, PG= prostaglandin, TX= tromoxane, LT= leukotriene, LX=lipoxin, EAE= experimental autoimmune encephalomyelitis, TMEV= Theiler's murine encephalomyelitis virus.

COX-2 in the biological mechanisms underlying the death of oligodendrocytes. Moreover, COX-2 is also expressed by inflammatory cells like macrophages and microglia that are located at active lesions (17). These data are in line with previous findings showing that COX-derived prostaglandins are excessively produced in the central nervous system of multiple sclerosis patients. The levels of prostaglandins PGD_2, PGE_2, and PGF_2, and prostacyclin PGI_2, were upregulated in the cerebrospinal fluid of patients during relapsing and remitting phases (18–20). PGE_2 levels were also elevated in lymphocytes extracted from the peripheral blood of patients; the highest levels were reached at the onset of the disease or just before symptoms, suggesting that PGE_2 could be involved in disease initiation (21).

As far as the metabolism of arachidonic acid by LOX enzymes is concerned, the levels of LTB_4 and LTC_4 in the cerebrospinal fluid of multiple sclerosis patients were elevated (18, 22). The same authors, in their second publication on the same topic, were able to replicate the results for LTB_4, but not for LTC_4, LTD_4, and LTE_4 levels (23). Overall, these data have suggested that, in multiple sclerosis, the metabolism of arachidonic acid through 5-LOX enzymatic activity was augmented. In 2010, a study, conducted in postmortem white matter specimens of multiple sclerosis patients, identified the *5-LOX* gene as a top risk gene for multiple sclerosis (24).

ARACHIDONIC ACID PATHWAY ACTIVATION IN ANIMAL MODELS OF MULTIPLE SCLEROSIS

The arachidonic acid metabolic pathway is activated in three different animal models of multiple sclerosis: the experimental autoimmune encephalomyelitis (EAE), the Theiler's murine encephalomyelitis virus (TMEV), and the cuprizone model (see Table 1 for details of primary data). In the EAE model, the upstream enzyme $cPLA_2$ has been shown to play a key role in the pathogenesis of the disease as $cPLA_2$ knockout mice and naïve mice treated with a $cPLA_2$ specific inhibitor were both resistant to EAE induction (25, 26). Downstream $cPLA_2$, COX-2, inducible PGE_2 synthase, and PGE_2 levels were all increased in the brain of EAE mice (27). COX-2 was expressed in the resident microglia, infiltrating macrophages, and endothelial cells of the brain of EAE mice (28–29). Concerning the four receptors of PGE_2, EP1, EP2, and EP4 were upregulated by one-, two-, and threefold, respectively (30). EP2 and EP4 have been implicated in the stimulation of lymphocytes CD4+ release and their activation in EAE model (30). Moreover, COX-1 expression and PGI_2 levels were upregulated in the brain of EAE mice, whereas the concentration of PGD_2 was downregulated, and the concentration of $PGF_{2\alpha}$ was unchanged (27). However, one study conducted in a chronic relapsing type of EAE showed conflicting findings. While the increase of COX-1, COX-2, and PGE_2 was confirmed, the PGD_2 levels remained unchanged in all the analyzed brain tissues (cerebral cortex, cerebellum, and spinal cord) (31). Interestingly, the increase of COX-2 expression and PGE_2 levels was observed in early stages of the disease (31), suggesting a pathogenic role.

In the TMEV model, COX-2 expression was observed in the spinal cord (15). Specifically, COX-2 was expressed in oligodendrocytes undergoing apoptosis as indicated by immunohistochemistry experiments that found colocalization of the COX-2 protein and the apoptotic mediator caspase-3. These data were confirmed

in a further study published in 2010 (16). The latter also showed that COX-2 mediates mechanisms of excitotoxicity against cultured oligodendrocytes (16). COX-2 and PGE_2 gene expression were also found in primary cultures of astrocytes from TMEV-infected mice (32). The inhibition of PGE_2 signaling at a downstream level using AH23848, which is a mixed EP1 and EP4 inhibitor, resulted in decreased pathogenesis of demyelinating disease (about 20% decrease) and severity of viral load (about 85% decrease) in the central nervous system (33).

Similar results were obtained in the cuprizone model of demyelination. Cuprizone takes about 5 to 6 weeks to induce a maximum demyelination in the brain, but oligodendrocytes express apoptotic markers earlier, starting from the first week of intoxication (34). In the brain of cuprizone-treated mice, both COX-1 and COX-2 were significantly upregulated, but the change in the expression showed different courses (34). COX-2 gene expression was found to be upregulated in the early phases of the cuprizone treatment when demyelination was not yet detectable, whereas COX-1 was upregulated later on at the peak of astrogliosis and microglia and/or macrophages activation concomitantly with severe demyelination (34). Interestingly, this observation led to the hypothesis that COX-2 precedes oligodendrocytes loss and is involved in the apoptotic processes. COX-2 was expressed in apoptotic caspase-3-expressing oligodendrocytes as early as after 1 week of cuprizone treatment (35). Further investigation in the COX-2 pathway showed that the cortical levels of several prostaglandins (PGE_2, PGD_2, PGI_2, and TXB_2), were upregulated (34, 35). The increase in PGE_2 concentration was more than the other prostaglandins, and the expression of its receptors, EP1, EP2, and EP4, was upregulated at the peak of demyelination (35). Interestingly, only EP2 protein expression was increased in the early stage, after 1 week of cuprizone treatment, and has been implicated in the initiation of demyelination and oligodendrocytes loss (35).

Regarding LOXs, there is an increasing consent supporting the role of 5-LOX and its downstream products in the mechanisms of immune cell recall in the brain, and in the development of axonal damage and of motor disabilities. The *5-LOX* gene was found to be a top risk gene in EAE (24). The brain concentrations of 5-LOX products, LTB_4 and LTD_4, were upregulated (18, 22–23), and favored the migration of inflammatory cells and lymphocytes in the brain of EAE mice (36–38). In the cuprizone model, the brain expression of 5-LOX was highly increased (39). In addition, 5-LOX has been implicated in cuprizone-mediated axonal damage and motor dysfunction development (39). Overall, the data generated from the animal research indicate that the arachidonic acid pathway contributes to the development of multiple sclerosis–like pathology, especially via COX-2 and 5-LOX metabolism.

Anti-inflammatory Therapy in Multiple Sclerosis

Arachidonic acid–mediated inflammation is typically inhibited with nonsteroidal anti-inflammatory drugs (NSAIDs). NSAIDs have variable specificity against the two isoforms of COX. While some NSAIDs (e.g., ibuprofen, indomethacin, and naproxen), have mixed inhibitory effect on both COX-1 and COX-2 others, like the coxibs (e.g., celecoxib, rofecoxib, and valdecoxib) and nimesulide, specifically inhibit COX-2 (40). NSAIDs have been administered to patients affected by

multiple sclerosis to counteract symptoms related to flu, but no clinical trials have ever evaluated whether NSAIDs could reduce multiple sclerosis pathology as well. Animal models of multiple sclerosis have demonstrated the beneficial effects of NSAIDs. Furthermore, the pharmacological inhibition of LOX-mediated metabolism of arachidonic acid exerts some beneficial effects. The following paragraphs describe the available evidence on the potential of COX and LOX inhibitors as therapeutics for multiple sclerosis.

NSAIDs TREATMENT IN PATIENTS AFFECTED BY MULTIPLE SCLEROSIS

It is not known whether NSAIDs have an inhibitory effect on the pathology of multiple sclerosis. To date, NSAIDs have been administered to patients to treat flu-like symptoms without taking into consideration of their potential role in oligodendrocytes survival and myelin protection (41–46). Nevertheless, some NSAIDs were shown to ameliorate fatigue (approximate percentage of improvement: 10–20% with aspirin, 30% with naproxen, and 20% with ibuprofen) and improve cognitive abilities (approximate fold change of improvement: 1-fold with naproxen, 0.5-fold with ibuprofen, and 2-fold with acetaminophen) (46, 47). It could be hypothesized that these effects may be secondary to the attenuation of brain pathology due to NSAIDs treatment, as suggested by the following data from experimental models of multiple sclerosis.

EFFECT OF NSAIDs IN ANIMAL MODELS OF MULTIPLE SCLEROSIS

Non-selective COX inhibitors and COX-2 selective drugs have shown protective effects in EAE, cuprizone and TMEV murine models of multiple sclerosis. In the EAE model, mixed COX-1/2 inhibitors (indometacin and naproxen) delayed the onset (about 8 days delay with naproxen) and the severity of the disease (about 30% improvement with indometacin and 70% with naproxen) (26, 48, 49). In the cuprizone model, COX-1 knockout mice normally develop demyelination in the same extent as matched wild type mice, indicating that COX-1 is not involved in the demyelination process. Conversely, knocking out the *COX-2* gene inhibited demyelination (about 40% inhibition in the corpus callosum and complete recovery in the cortex) and restored motor functions (35).

Selective targeting of COX-2 has provided a large number of evidence, supporting the prominent role of this isoform in disease initiation and severity. The administration of selective COX-2 inhibitors (LM01, LM08, LM11, and NS398), or coxibs (rofecoxib, celecoxib, and lumiracoxib) interfered with EAE induction by decreasing physical dysfunctions, inflammation, and demyelination; the protective effects of these compounds were mediated through the inhibition of adhesion and chemoattractant molecules, and the reduction of monocyte infiltration (48–51). Specifically, LM01, LM08, LM11, and NS398 inhibited the paralysis period (percentage inhibition: 48, 95, 76, and 43, respectively), inflammation (percentage inhibition: 85, 84, 78, and 81, respectively), and demyelination (percentage inhibition: 74, 67, 53, and 61, respectively) (50). Celecoxib prevented EAE induction, reduced the expression of adhesion and chemoattractant

molecules (histological nonquantitative data), and inhibited the number of infiltrating monocytes (49). Rofecoxib and lumiracoxib reduced inflammation by 90% and 85%, respectively (51).

In the TMEV model, the COX-2 selective inhibitor CAY10542, reduced demyelination by 25%, and prevented the death of oligodendrocytes (16). The efficacy of COX-2 targeting has been confirmed in the cuprizone model as well, as celecoxib greatly reduced demyelination (about 30% reduction in the corpus callosum and complete recovery in the cortex) along with a full recovery of motor abilities (35). In this model, COX-2 expression exerts deleterious effects on the oligodendrocytes through the production of PGE_2, with in turn contributes to loss of oligodendrocytes by interacting with the EP2 receptor: the administration of an EP2 antagonist to cuprizone mice showed similar protective effects as the ones induced by celecoxib (35).EAE mice treated with an inhibitor of $cPLA_2$ showed marked beneficial activity (about 85% inhibition of disease severity) (26). Because of this observation, the question arises whether, the protective effect is mediated merely through the inhibition of the COX pathway or the inhibition of LOX activity is also involed. It has been shown that 5-LOX selective inhibition delayed the onset of EAE by about 5 days (26). Similarly, in the cuprizone model, 5-LOX inhibition resulted in reduced axonal pathology and ameliorated motor disabilities without any improvement in the demyelination severity (39). Overall, these data suggest that COX-2 and 5-LOX inhibition have some nonoverlapping activities (52).

NSAIDs Administration: Future Perspectives

Most of the currently available pharmacological medications for multiple sclerosis counteract the activity of the autoimmune system. Lymphocytes are the leading factors in the autoimmune-mediated mechanisms implicated in the disruption of myelin proteins and the death of oligodendrocytes. First-generation drugs (interferons and glatiramer acetate) and second-generation drugs (fingolimod, mitoxantrone, rituximab, ocrelizumab, ofatumumab, and others) reduce disease severity, progression, and relapses; their main mechanism of action include sequestration of lymphocytes in the lymph node, and reduction of their access to the brain (53–56). However, these drugs do not directly target the arachidonic acid metabolism. Based on the literature, NSAIDs are currently administered to patients if flu-like symptoms occur. However, growing evidence supports the hypothesis that COX-2 and 5-LOX enzymes promote downstream mechanisms that ultimately lead to oligodendrocyte degeneration and axon pathology, respectively, and that both contribute to the development of motor disabilities. The combination of COX-2 and 5-LOX selective inhibitors has the potential to improve multiple sclerosis pathology. Moreover, multiple sclerosis has been associated with platelet activation and augmented cardiovascular risk, which are considered as causal factors in the pathogenesis of the disease (57, 58). Interestingly, it has been recently observed that peripheral blood platelets of patients highly express COX-2 (58). In the light of these evidence, the administration of COX-2 selective NSAIDs could reduce both cardiovascular risk and the progression of multiple sclerosis.

Conclusion

Several pharmacological studies, conducted in experimental animal models of multiple sclerosis, suggest that NSAIDs that selectively inhibit the COX-2 isoform represent promising medications for reducing oligodendrocytes apoptosis, demyelination, and motor dysfunction. In addition, it is suggested that 5-LOX inhibitors could be beneficial to counteract axonal pathology and to inhibit motor disabilities as well. The coadministration of COX-2 and 5-LOX inhibitor is a promising way forward for multiple sclerosis treatment.

Conflict of interest: The authors declare no potential conflicts of interest with respect to research, authorship, and/or publication of this article.

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