# Molecular and therapeutic approach of specialised pro-resolving mediators in central nervous system diseases

## Enfoque molecular y terapéutico de mediadores pro-resolutivos especializados en enfermedades del sistema nervioso central



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**Abstract**

Neuroinflammation is a key pathophysiological hallmark across a spectrum of debilitating neurological disorders, contributing significantly to disease progression and disability. This pervasive inflammatory state arises from an imbalance in lipid mediators, a class of bioactive molecules derived from fatty acids that orchestrate both pro- and anti-inflammatory responses. Specialised pro-resolving lipid mediators (SPMs), a subclass of lipid mediators synthesised from omega-3 and omega-6 polyunsaturated fatty acids, play a pivotal role in orchestrating the timely resolution of inflammation. These SPMs, classified into resolvins, protectins, lipoxins, and maresins, actively promote the termination of inflammatory cascades and tissue repair. Recent research has unveiled a compelling link between dysregulated SPM production and the relentless neuroinflammation observed in various central nervous system pathologies, including Alzheimer's disease, amyotrophic lateral sclerosis, epilepsy, multiple sclerosis, and cerebrovascular disease. This crucial finding underscores the potential for SPMs as novel therapeutic targets, paving the way for a paradigm shift in managing neurological disorders. This review delves into the intricate molecular mechanisms of SPMs, their multifaceted roles within the CNS, their implications in neurological disease pathogenesis, and their burgeoning potential as therapeutic targets in neuroinflammation resolution.

**Keywords:** Neuroinflammation, CNS diseases, SPMs, Lipoxins, Resolvins, Maresin, Neuroprotectin, Inflammation.

## Resumen

La neuroinflamación es un sello fisiopatológico clave en una variedad de trastornos neurológicos debilitantes, contribuyendo significativamente a la progresión de la enfermedad y la discapacidad. Este estado inflamatorio generalizado surge de un desequilibrio en los mediadores lipídicos, una clase de moléculas bioactivas derivadas de ácidos grasos que regulan tanto las respuestas proinflamatorias como antiinflamatorias. Los mediadores lipídicos pro-resolutivos especializados (SPMs, por sus siglas en inglés), una subclase de mediadores lipídicos sintetizados a partir de ácidos grasos poliinsaturados omega-3 y omega-6, desempeñan un papel crucial en la resolución oportuna de la inflamación. Estos SPMs, clasificados en resolvinas, protectinas, lipoxinas y maresinas, promueven activamente la terminación de las cascadas inflamatorias y la reparación tisular. Investigaciones recientes han revelado un vínculo convincente entre la producción desregulada de SPMs y la neuroinflamación persistente observada en diversas patologías del sistema nervioso central, como la enfermedad de Alzheimer, la esclerosis lateral amiotrófica, la epilepsia, la esclerosis múltiple y las enfermedades cerebrovasculares. Este hallazgo crucial subraya el potencial de los SPMs como nuevos objetivos terapéuticos, abriendo el camino para un cambio de paradigma en el manejo de los trastornos neurológicos. Esta revisión profundiza en los intrincados mecanismos moleculares de los SPMs, sus roles multifacéticos dentro del SNC, sus implicaciones en la patogénesis de enfermedades neurológicas y su creciente potencial como objetivos terapéuticos en la resolución de la neuroinflamación.


**Palabras clave:** Neuroinflamación, enfermedades del SNC, SPMs, Lipoxinas, Resolvinas, Maresinas, Neuroprotectina, Inflamación.

## Introduction

Neurodegenerative diseases, cerebrovascular disease, and traumatic brain injuries are significant public health issues. The annual economic burden generated by these disorders averages $148 billion just in the United States, and this is perpetuated by the hundreds of millions of cases that continue to emerge worldwide[1–4]. In 2016, neurological disorders were the primary cause of years of life lost due to illness, disability, or premature death and the second most important cause of death worldwide. The four major neurological diseases contributing to a high year lived with disability were stroke (42.2%), migraine (16.3%), Alzheimer's disease (AD), other dementias (10.4%), and meningitis (7.9%)[1].

From an immunobiological perspective, a common trait of many neurological disorders is the marked imbalance between pro-inflammatory and anti-inflammatory lipid mediators, expressed through the characteristic neuroinflammation described in these disorders[5-7]. These lipids, just like anywhere else in our body, play a crucial role in the translocation of endocrine, autocrine, and paracrine signals, the activation/inactivation of receptors, and as precursors of bioactive mediators known as lipid mediators[8,9].

Some well-known examples are prostaglandins and leukotrienes synthesised from polyunsaturated fatty acids present in cell membrane phospholipids, and which are partly responsible vascular tone and vascular permeability maintaining, platelet aggregability, and the immune cells chemotaxis[10]. Similarly, prostaglandins and leukotrienes stimulate the synthesis of SPMs, a series of bioactive lipid compounds (resolvins, protectins, maresins, and lipoxins) that are of utmost importance for the resolution of inflammation and, consequently, for homeostasis restauration in inflamed tissues[11].

This review aims to provide a detailed molecular overview of SPM synthesis and their signalling pathways, with an emphasis on the role these compounds play in Alzheimer's disease, Parkinson's disease, amyotrophic laeteral sclerosis (ALS), multiple sclerosis (MS), epilepsy, and cerebrovascular disease. Potential therapeutic targets and their possible impact on treating these diseases will be analysed.

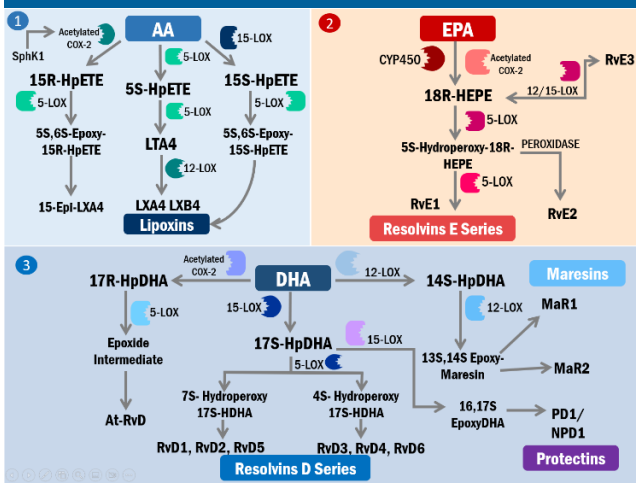
### Specialised pro-resolving lipid mediators: biosynthesis and function

SPMs are bioactive compounds derived from omega-3 and omega-6 polyunsaturated fatty acids (PUFAs), responsible for fulfilling various biological functions involved in the resolution of inflammation[12,13]. Currently, four families of SPMs have been described: 1) Lipoxins, 2) Resolvins, 3) Protectins, and 4) Maresins. The biosyn-

thesis of these compounds involves several processes that require the addition of molecular oxygen to PUFAs through the involvement of enzymes such as lipoxygenase (LOX), cyclooxygenase-2 (COX-2), and, to a lesser extent, the cytochrome P450 system[14].

SPMs exert their positive resolution functions in the inflammatory response by binding to transmembrane receptors coupled to G-proteins and the signalling pathways they share, such as intracellular phosphorylation cascades and gene regulation on the increase of intracellular calcium, with the unique exception of PD1 (Figure 1)[15,16].

**Figure 1. Pro-resolving specialised lipid mediators biosynthesis pathways.**




### *Lipoxins*

Serhan, Hamberg, and Samuelsson initially identified the lipoxin family in 1984[17] while studying activated neutrophils, observing that they stimulated the production of superoxide anion (O2–) and the degranulation response. Subsequent studies found that lipoxins mainly dampen and resolve inflammation, exhibiting anti-inflammatory signalling properties. Lipoxins are AA (ω-6) that contain three hydroxyl groups and four double bonds, unique characteristics that distinguish them from other SPMs such as resolvins, protectins, and maresins, which are, omega-3 fatty acids metabolites. This group includes lipoxin A4 (LXA4) and lipoxin B4 (LXB4) produced by 5-lipoxygenase (5-LOX), 15-lipoxygenase (15-LOX), and 12-lipoxygenase (12-LOX) through two main pathways. Additionally, lipoxin epimers are formed under aspirin treatment[18].

For the first biosynthetic pathway to occur, the interaction between neutrophils and platelets during the inflammation process is necessary, where within the neutrophil, 5-LOX catalyse the oxidation of AA at position 5, turning it into leukotriene A4 (LTA4), an intermediate product that once released, is picked up by platelets where it is quickly subjected to another oxygenation process mediated by 12-LOX at position 15, resulting in LXA4 and LXB4, the final bioactive compounds[17]. On the other hand, the second pathway begins with the oxygenation of AA, this time mediated by 15-LOX, generating 15S-hydroperoxyeicosatetraenoic acid (15S-HpETE), an intermediate substrate that is in turn transformed by the activity of 5-LOX into 5S, 6S, 15S-epoxytetraene, leading LXA4 and LXB4 production by hydrolisis. This pathway commonly occurs in in the alveolar macrophages, monocytes, and eosinophils where 15-LOX can be abundantly found[19].

Regarding the lipoxin epimers, these compounds are formed under the effect of aspirin, which by acetylating COX-2, changes its enzymatic function from endoperoxidase to lipoxygenase, being able to convert AA into 15-(R) hydroxyeicosatetraenoic acid (15R-HETE), and subsequent metabolised by 5-LOX to form 15-Epi-LXA4 and 15-Epi-LXB4, known as aspirin-triggered lipoxins (ATL)[17]. It has recently been discovered that 15-Epi-LXA4 is also biosynthesised in the nervous system through an alternative pathway attributed to the activity of sphingosine kinase 1 (SphK1). Lee et al. demonstrated that this enzyme catalise COX-2 acetylation and produces 15-Epi-LXA4 using acetyl-CoA in mice's neuronal tissue[20,21].

The ALX/FPR2 receptor is responsible for LXA4 effects, whose signalling pathway triggers the attenuation of nuclear factor κB (NF-κB) and blocks the phosphorylation of p38 ERK and JNK, demonstrating neuroprotective functions mediated jointly by the reduction of leukocyte infiltration and astrocytic activation, reducing the production of TNFα, IL-1b, and leukotrienes[22,23–25].

### Resolvins (Rv): E and D Series

The ω-3 EPA acid is the precursor to the E series of resolvins (Rv), which were first identified by Serhan, Clish, and Brannon in 2.000 when noted their presence as potent leukocyte infiltration and migration inhibitors induced by the injection of TNF-α in inflammatory exudates in rats[26]. These bioactive compounds are endogenously biosynthesised through the interaction of vascular endothelial cells with leukocytes during the inflammatory process, resulting in the formation of RvE1, RvE2, and RvE3, which are characterised by having three hydroxyl groups and five double bonds in their structure[27]. Initially in endothelial cells, EPA can be metabolised either by cytochrome P450 or by aspirin-acetylated COX-2 into 18R-hydroperoxyeicosapentaenoic acid (18R-H(p)EPE), which through peroxidases is reduced to 18R-HEPE. Then, this intermediate product is released and either taken up by neutrophils and directly converted into RvE1 or RvE2 in the presence of 5-LOX[28,29] or transformed into RvE3 by the action of 12/15-LOX in eosinophils[30].

Regarding their receptors and signalling pathways, a receptor has only been discovered for RvE1, which binds to the chemerin receptor 23 (ChemR23 / ERV1) and BLT1. ChemR23/ERV1 is found in tissues such as the spleen and bone marrow and is also present in glial cells and neurons, playing a regulatory role in leukocyte pro-

duction[31]. Its activation by RvE1 triggers pro-resolving effects mediated by the activation of PI3K and ERK. This activation, in turn, triggers the phosphorylation of Akt and ribosomal protein S6, which then induces phagocytosis along with the inhibition of the TNFα-induced NF-κB signalling pathway, resulting in a decrease in gene expression, leukocyte infiltration, and the production of added pro-inflammatory cytokines along with an increase in efferocytosis activity[32]. Conversely, RvE1 acts on BLT1 as a partial agonist that competes for a binding site with LTB4, decreasing its inflammatory effect[33].

Unlike the RvE series, the precursor of the RvD series is the ω-3 fatty acid DHA, giving it a different structure endowed with three hydroxyl groups and six double bonds. Discovered for the first time in 2003 by Hong et al.[34] through lipidomic analysis in human blood and rodent brains, new bioactive compounds with anti-inflammatory effects were observed. The synthesis pathway of RvD begins with the 15-LOX mediated enzymatic conversion of DHA to 17S-hydroperoxyDHA (17S-H(p)DHA), catalysing carbon 17 oxidation. From this point, the final product obtained will dependent on hydroxylated carbon by neutrophils's 5-LOX, resulting in an intermediate 7(S)-hydroperoxy-17(S)-HDHA adduct, and then, resolvin RvD1, RvD2, and RvD5 synthesis if carbon seven is hydroxylated, or 4(S)-hydroperoxy-17(S)-HDHA followed by the synthesis of resolvin RvD3, RvD4, and RvD6 if carbon four is hydroxylated instead[35]. Likewise, aspirin-acetylated COX-2 also leads to the conversion of DHA into 17R-Hydroxyperoxy-DHA (17R-H(p)DHA), which can then be metabolised by 5-LOX resulting in aspirin-induced resolvins (AT-RvD)[36].

Resolvins Conjugated in Tissue Regeneration (RCTRs) are a newly discovered group found in murine exudates and human blood that stimulate tissue repair in vivo, enhance macrophage-mediated phagocytosis, and reduce the recruitment of cytokines and PMN, both in vivo and in vitro[37]. This group is composed of RCTR1, which is formed by the bonding of glutathione with the intermediate epoxide of RvDs, and RCTR2 and RCTR3, formed by the action of γ-glutamyltranspeptidase and peptidases from RCTR1[38].

The biological functions of this group are mediated by the ALX/FPR2, GPR32/DRV1, and GPR18/DRV2 receptors. Similar to LXA4, RvD1 also binds to the ALX/FPR2 receptor, where it acts to regulate miRNA synthesis involved in the expression of pro-inflammatory genes, demonstrating the variety of ways the same receptor can be engaged in the resolution of inflammation[39]. Likewise, RvD1 acts on the GPR32/DRV1 receptor, as do most of the resolvins from the D series: RvD3, RvD4, RvD5, and RvD6. The interaction between RvD1 and GPR32/DRV1 increases the synthesis of IL-10; miR146b, which inhibits the transcription of NF-κB; and finally miR-219, which regulates the expression of 5-LOX and decreases the levels of LTB4 and miR-208a, which inhibits the transcription of the suppressor factor (PDCD4)[40,41]. On the other hand, GPR18/DRV2 -the RvD2- receptor is primarily limited to bone marrow and lymphoid tissue[35]. The binding of RvD2 to its receptor increases the intracellular phosphorylation levels of AMPc and CREB, ERK1/2, and STAT3, activating intracellular signalling pathways that stimulate phagocytosis and efferocytosis[42].

***Protectins***

Identified along with the D series of resolvins in 2003 by Hong et al. [36], it was observed that DHA was also converted in vivo into compounds endowed with two hydroxyl groups and six double bonds, which exhibited anti-inflammatory effects such as a reduction in leukocyte infiltration and cytokine production both in vitro and in vivo, earning the name protectins. They are also known as neuroprotectins (NPD1) when generated by nerve cells due to their potent protective effect on the retina, brain, and pain management, highlighting their significant involvement in various CNS diseases[43]. In addition to PD1/NPD1, this group includes PDX, an isomer of PD1 with a lesser anti-inflammatory biological response from double lipoxygenation[44]. In 2015, the protectins conjugated in tissue regeneration (PCTR), including PCTR1, PCTR2, and PCTR3, were added to this group identified for resolving E. coli infections in rat and human spleens[45].

Like the D series of resolvins, protectins are also biosynthesised from DHA once it is metabolised into 17S-H(p)DHA. 15-LOX catalyses the synthesis of the intermediate epoxide 16[17] epoxy DHA, and its subsequent hydrolysis leads to the production of PD1. 17S-H(p)DHA can also be oxidised a second time by 5-LOX to form 4S,17S-diHDHA and 7S,17S-diHDHA, 17S-diHDHA compounds, which are similar in structure to PD1 but exhibit less bioactivity than the latter[32,46]. As described in the previous SPM groups, aspirin-acetylated COX-2 also induces the synthesis of AT-PD1[47]. PD1 receptor is GPR37, a protein expressed in macrophages and nervous system cells. Unlike all previously mentioned receptors, the binding of PD1 to GPR37 does not trigger a phosphorylation cascade but rather increases intracellular calcium levels, leading to the activation of calcium-dependent signalling pathways and culminating in the stimulation of phagocytosis and regulation of cytokine production[16,48].

**Maresins**

Macrophages are one of the most important cells involved in inflammation due to their diverse immune functions, the principal being phagocytosis. However, Serhan et al.[49] 2008 discovered that they are also involved in the production of SPMs, as it was evidenced that macrophages isolated from exudates in mice converted DHA into products identified by mass spectrometry, which contained in their structure, like protectins, two hydroxyl groups and six double bonds, which were labelled as maresins (macrophage mediator for resolving inflammation). This family comprises MaR1, MaR2, and the maresins conjugated in tissue regeneration (MCTR)[50]. In terms of its receptor, MaR1 shares binding to the BLT1

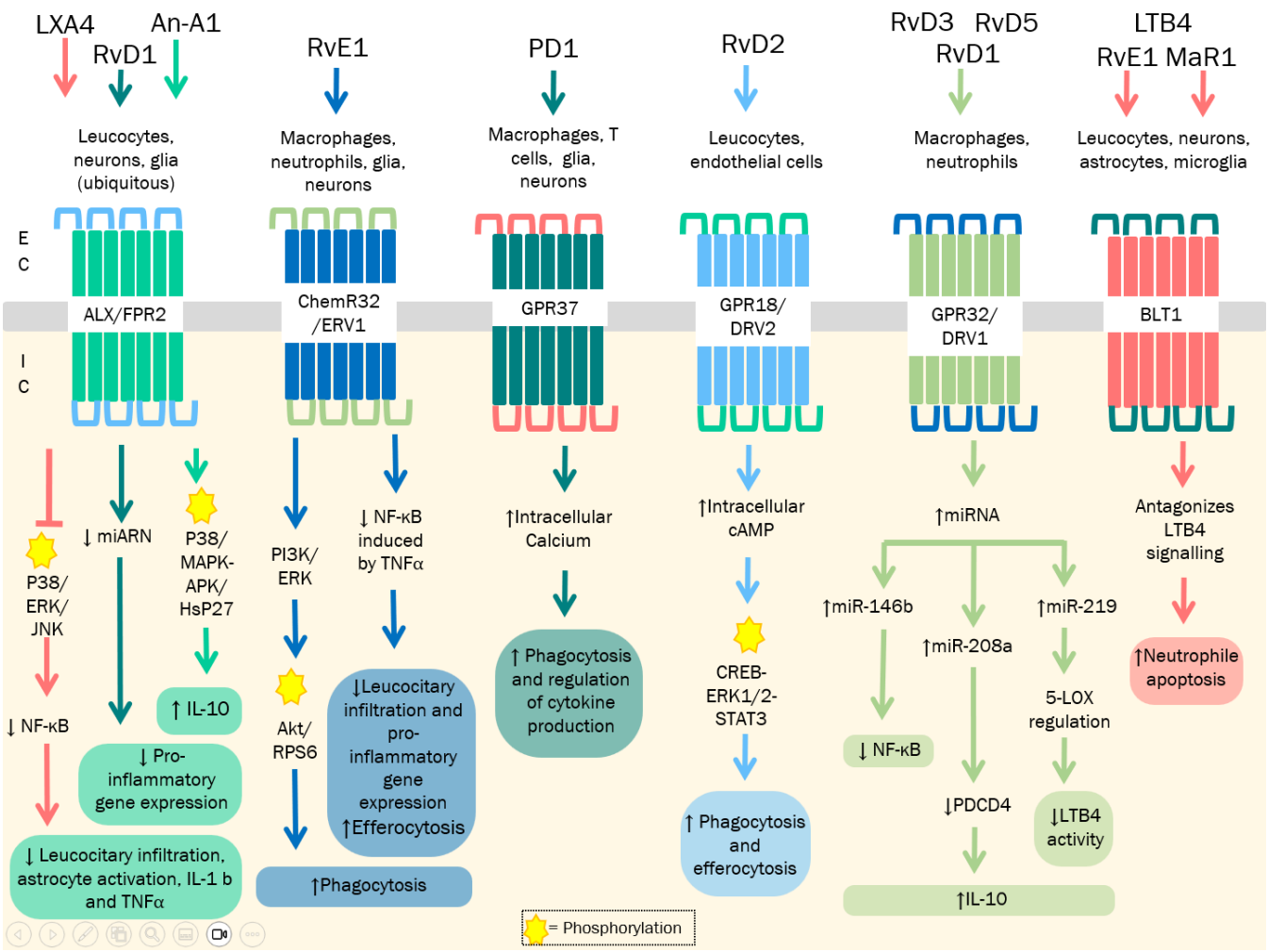
receptor along with RvE1. In this case, MaR1 antagonises the activation of LTB4 from BLT1, inhibiting LTB4 signalling and biological functions and stimulating apoptosis of neutrophils[51], while the receptor for MaR2 has not yet been identified. The biosynthesis of these compounds is marked by the oxidation induced by 12-LOX of DHA, resulting in the production of 14S-HpDHA, followed by an intermediate synthesis of 13,14S-epoxy-maresin. This epoxy-intermediate undergoes enzymatic hydrolysis and converts into MaR1 or MaR2 when metabolised by the soluble epoxide hydrolase (sEH)[5,52]. On the other hand, 13S-14S-epoxy-maresin is also a substrate for leukotriene C4 synthase (LTC4S) and glutathione S-transferase MU 4 (GSTM4), which form MCTR1, which in turn serves as a precursor to MCTR2 and MCTR3[53].

### Role of lipid mediators in CNS diseases

A common aspect shared by neurodegenerative diseases, ageing, and neurological disorders is neuroinflammation, a phenomenon with a protective purpose intended to regulate pathological processes occurring in the CNS, largely through the action of activated microglia and astrocytes. However, effective resolution is required to prevent it from becoming harmful and progressing to chronic neuroinflammation[54–56]. The activation of microglia in neuroinflammation triggers a series of immune responses that induce the production of chemokines, cytokines, and free radicals capable of perpetuating the inflammatory process, as well as adhesion molecules such as VCAM-1 and ICAM-1 that induce apoptosis and death of dopaminergic neurons[56]. Many studies have suggested that the cause of chronic inflammation of the brain and spinal cord following trauma, acute injuries, or as a consequence of neurodegenerative disease could be directly related to a defect in inflammation resolution[57]. Additionally, it has been demonstrated that the dysregulation of SPM production results in inadequate resolution of inflammation, leading to the inevitable progression of various CNS diseases[14]. Therefore, the current therapeutic horizon aims to reduce microglial activation, inhibit pro-inflammatory mediators, and promote neuronal survival to prevent chronic inflammation and simultaneously decrease the generation and progression of neurodegenerative pathologies. In this context, SPMs enter as potential therapeutic targets capable of mediating the endogenous resolution of the inflammatory process[58] (see Figure 2).



**Figure 2. Schematic representation of pro-resolving specialised lipid mediators, receptors and biological actions.**



***Alzheimer's Disease***

Neuroinflammation plays a fundamental role in the pathophysiology of Alzheimer's disease from its onset. It has been supported by the finding of mutations in microglial genes or those of innate immune cells, which promote an increase in their activity and the development of the inflammatory response[59]. Neuroinflammation is initially beneficial in AD due to the activity of the CNS's resident immune cells, specifically, the microglia pro-inflammatory M1 phenotype, activated by amyloid β leading to Aβ phagocytosis in an attempt to maintain cerebral homeostasis[60,61]. However, when inflammation becomes chronic, it is the main trigger for neurodegeneration and the cognitive decline present in people with Alzheimer's disease[62]. When brain inflammation becomes chronic, the efficacy of microglial phagocytosis decreases, possibly due to a dysfunction of Toll-like receptors[63–66]. Indeed, apoptosis of microglia induced by the accumulation of lysosomal Aβ that exceeds the cell's clearance threshold could directly contribute to Aβ deposits and the acceleration of plaque formation[67].

Despite the decrease in phagocytic efficiency, the ability of microglial cells to secrete pro-inflammatory cytokines such as IL-1, IL-6, and TNF-α seems unaffected[63,68]. As these pro-inflammatory agents exacerbate neuroinflammation, peripheral macrophages are recruited, and a marked increase in the synthesis of amyloid precursor protein (APP), reactive oxygen species, and chemokine secretion[69]. Far from being beneficial, these events promote cytotoxicity and neurodegeneration, aggravating the progression of the disease[70].

Similarly, there is substantial evidence suggesting that the chronic pro-inflammatory state found in the brains of AD patients is due, at least in part, to the imbalance between SPMs and pro-inflammatory lipid mediators, with the balance tipped in favour of the latter[71–74]. Following this line of thought, several animal models and studies of patients with AD have demonstrated a persistent alteration in SPM levels[75]. In a study by Kantarci et al., significantly lower levels of RvE1, RvD2, and LXA4 were found in the hippocampus of transgenic 5xFAD mice compared to non-transgenic controls[72]. Additionally, in a study by Dunn et al., where brain tissue from transgenic 3xTg-AD mice was analysed, an age-related decrease in LXA4 levels in the brain was observed[76].

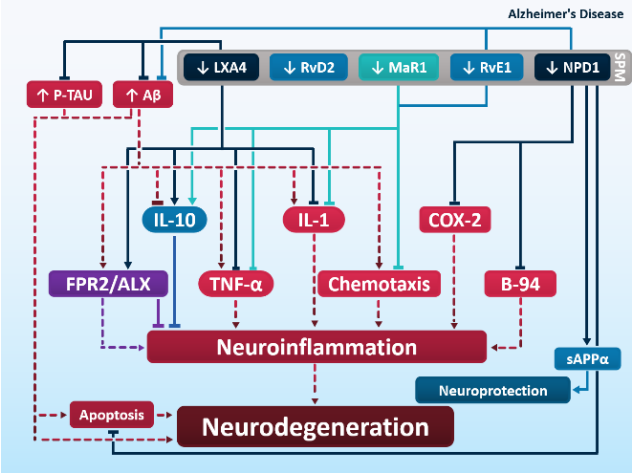
The resolution of inflammation is a regulated and biochemically active process in which SPMs play a significant role. Current evidence supports that in Alzheimer's disease, there are reduced levels of MaR1, RvD5, and NPD1, which leads to an altered pro-resolution process. All of this suggests that promoting the resolution of inflammation may influence the delay of cognitive decline in patients with this pathology[77].

Furthermore, in an in vitro study of murine neuron-microglia co-cultures, it was concluded that MaR1 down-regulated various pro-inflammatory mechanisms promoted by the Aβ42 peptide, such as microglial chemotaxis, increased pro-inflammatory cytokines like TNF-α, and decreased IL-10[77]. These events lead to the presentation of the following hypothesis: the decrease in MaR1 observed in the entorhinal cortex and hippocampus of AD patients directly contributes to prolonging the pro-inflammatory state characteristic of AD[73,78]. Additionally, it has been reported that in individuals with AD, levels of LXA4 decrease both in post-mortem hippocampal tissue and cerebrospinal fluid (CSF)[73]. Moreover, there is a notable increase in glial expression of ALX/FPR2, possibly driven by sustained neuroinflammation, making the tissue more sensitive in turn to LXA4, but also to other pro-inflammatory ligands binding to the same receptor, such as the Aβ peptide[79]. Thus, the deficiency of LXA4 could contribute to ongoing inflammation in this case[80–82].

On the other hand, in post-mortem studies of human brain tissue, a decrease in the levels of NPD1 and DHA was reported when studying the hippocampus of deceased AD patients[83]. Similarly, levels of NPD1 are also found to be reduced in the entorhinal cortex of AD patients[78]. Given that 15-LOX is a key enzyme in the biosynthesis of NPD1, the decrease in cerebral NPD1 in AD patients may occur due to a reduction in 15-LOX mRNA as a result of increased NF-κB-sensitive miRNA-125b in these AD patients[83,84].

The decrease mentioned above in NPD1 adds to the pathophysiological framework of AD, as NPD1 negatively regulates apoptosis and the expression of the pro-inflammatory element induced by COX-2 and TNF-α induced by Aβ42 (B-94)[85]. Additionally, NPD1 also inhibits the production of Aβ42 by negatively regulating β-secretase-1, an enzyme that synthesisesAβ from APP, and also activates α-secretase ADAM10, which in turn is responsible for the production of sAPPα derived from APP, a neuroprotective peptide[86,87] (see Figure 3).

**Figure 3. Specialised Pro-resolution Lipid Mediators in Alzheimer's Disease.**



**Parkinson's Disease**

The characteristic findings in PD are Lewy bodies composed of α-synuclein, there is experimental and postmortem evidence indicating that neuroinflammation plays a role in the pathogenesis of PD. In this regard, high levels of IL-6 have been associated with an increased risk of developing PD[88]. It is suggested that the origin of neuroinflammation in this disease is due to the chronic activation of microglia in the substantia nigra due to accumulations of α-synuclein, which triggers an increase in pro-inflammatory mediators, which have been shown to result in the exacerbation of damage and death of dopaminergic neurons[89].

Regarding the neuroinflammation observed in PD, the potential role of a deficiency in SPMs is of interest, which, while it could contribute to maintaining the pro-inflammatory state, has been studied little so far. However, several studies in laboratory models of PD demonstrate the beneficial effect of replenishing SPMs in this pathology. In this context, Dakian et al. found that in a transgenic rat model of PD overexpressing non-mutated human α-synuclein, there was a significant decrease in RvD1. Furthermore, treatment with RvD1 reduced neuroinflammation, restored dopaminergic neurotransmission, and prevented the subsequent development of neuronal deficits and motor deterioration[90]. Similarly, Xu et al. found beneficial effects of RvD1 in cell culture models of PD, concluding that RvD1 improved PD by suppressing inflammation[91]. Additionally, in another study by Tian et al., it was observed that intrathecal injection of RvD2 in a rat model of lipopolysaccharide-induced PD prevented the development of behavioural alterations and the activation of the TLR4/NF-κB pathway, supporting the benefit of SPMs in the treatment of PD, at least in animal models[92]. Moreover, there is evidence showing that in the early stages of PD in humans, in addition to an increase in pro-inflammatory cytokines IFN-γ, TNF-α, IL-4, and IL-10, levels of RvD1 in both CSF and plasma are drastically reduced compared to healthy subjects, although the levels of RvD2 do not appear to be diminished[93].

***Amyotrophic Lateral Sclerosis***

ALS is a degenerative disease characterised by progressive impairment of upper and lower motor neurons[94], exhibiting various clinical phenotypes, yet commonly presenting with weakness, spasticity, and, in some cases, cognitive deficits[95]. ALS is a complex genetic disorder, with some cases classified as familial and others as sporadic, representing the most common motor neuron disease in adults, with a prevalence of about 6 cases per 100,000 people. Unfortunately, ALS is a fatal and still incurable disease, with an average survival time of 3 to 4 years from onset to death[96]. Although the pathophysiological mechanisms of ALS are not fully understood, it is known that a hallmark of this disease is the aggregation of ubiquitinated protein inclusions within motor neurons. Various factors are involved in the progression of ALS, mainly alterations in proteostasis, RNA metabolism and DNA repair, mitochondrial dysfunction, axonal damage, excitotoxicity, oligodendrocyte degeneration, and neuroinflammation[94].

Regarding neuroinflammation, generalised microglial activation is characteristic of ALS. Although few studies are exploring the role of SPMs in ALS, a notable study by Cacabelos et al. concluded that in the early stages of ALS, excitotoxicity and oxidative stress increased DHA levels, as demonstrated by the increased expression of enzymes involved in its synthesis, leading to speculation that this could be a compensatory mechanism, necessary for the production of resolvin and neuroprotectin. Ultimately, this compensatory mechanism is overcome by the depletion of DHA, which then leads to neuronal dysfunction[97].

Furthermore, a cell culture study conducted by Ohuchi et al. reported that MaR1 promotes motor neuron survival by opposing oxidative stress and reducing cell death induced by endoplasmic reticulum stress[98]. Additionally, in another study by Liu et al., it was demonstrated that RvD1 inhibits the transcription and production of pro-inflammatory cytokines IL-6 and TNF-α in spinal cord macrophages from ALS patients[99].

***Epilepsy***

It has been shown that persistent neuroinflammation, caused partly by an endogenous anti-inflammatory mechanism dysfunction, is a plausible mechanism of epileptogenesis. Therefore, it is interesting to consider the role of SPM alteration in epilepsy[100-102]. In a study by Frigerio et al., seizures were induced in animal subjects with kainic acid, finding that the enzymes RvD2, RvD5, and LOX (Alox 5 and Alox 15 mRNA) were downregulated, and NPD1 was upregulated in the hippocampus of epileptic mice[102]. This increase in NPD1 could signify a compensatory response to seizures and their underlying causes, as this lipid mediator has been shown to play a neuroprotective role in many epilepsy studies, as it can provide protection for dendrites and dendritic spines during epileptogenesis, improve neuronal electrical activity, attenuate the onset, and limit the progression of the severity of seizures[103–105].

***Multiple Sclerosis***

Given the fundamental role that inflammation plays in MS, it is worth noting that SPM levels are altered in this disease, as demonstrated by a study of an MS mouse model conducted by Poisson et al., where it was found that PUFA metabolites necessary for SPM synthesis, omega-3 and omega-6 fatty acids, are reduced in the subjects studied[106,107]. Furthermore, in a study conducted by Wang et al., a decrease in RvD1 was observed in the CSF of MS patients compared to healthy controls, suggesting that dysfunctional inflammatory resolution could be involved in the progression of the disease[108]. Contrary to these results, a relationship has been established between the severity of the disease and levels of RvD1, which significantly increases in highly active MS[109].

A study by Kooij et al.[110] analysed the peripheral blood of patients from different hospitals in Italy, finding alterations in lipid mediators with different profiles, each associated with the progression and severity. Kooij et al. also found changes in the expression of enzymes and receptors associated with the synthesis of SPMs, which correlates with the stage of the disease and supports the role of these mediators in the resolution process of inflammation. This evidence suggested the potential therapeutic option of SPMs for these entities[110,111]. Currently, existing therapies for MS have not been completely effective in controlling inflammation or altering the natural course of the disease. Although SPMs and their role in inflammatory pathologies of the nervous system have been known since the early 21st century, they are still under-studied. However, they are recognised as potent mediators of inflammation's control and resolution process, making them a potential therapeutic option[111].



***Cerebral Infarction***

Recent studies indicate that a failure in local resolution mechanisms may underlie aberrant inflammation in cerebrovascular events. Among SPMs, the most studied concerning cerebral infarction are LXA4 and resolvins. It has been shown that these play a significant role in reducing cerebral oedema and improving sensory and motor function and higher brain functions, such as learning and memory[125-128].

While various macrophage activation phenotypes are known, several studies highlight the potential role of SPMs in shifting macrophages from a pro-inflammatory M1 phenotype to an anti-inflammatory M2 phenotype through binding to GPR32. Moreover, the expression of 12/15-LOX, detected in neurons and endothelial cells after cerebral ischemia[112] and its arachidonic acid-derived products, specifically LXA4 and RvD1, can directly influence the activation of the M2 phenotype, whereas their deficiency induces an inflammatory state[41,113,114]. Additionally, 15-LOX alone might have a beneficial effect by promoting angiogenesis post-cerebral infarction[115].

Another important aspect in the resolution of acute inflammation is the activation of endothelial cells (EC), which express SPM receptors on their surface. An example of this is the expression of ALX/FPR2, which acts by reducing the recruitment and adhesion of polymorphonuclear cells, negatively regulating adhesion molecules VCAM-1 and E-selectin during the resolution phase of the inflammatory process[116,117]. On the other hand, lipid mediators such as sphingosine-1-phosphate (S1P) activate its receptor S1P receptor 2 on the endothelium and have been observed to increase cerebrovascular permeability, leading to intracerebral haemorrhage and exacerbated neuroinflammation; following the administration of fingolimod, an S1PR antagonist, and Siponimod, sphingosine l-phosphate receptor modulators, ischemia and brain damage are attenuated[118].

In studying the impact of middle cerebral artery occlusion and the consequences of reperfusion in rats, a significant decrease in endogenous synthesis of RvD2 was found. Another important finding was that the GPR18 antagonist O-1918 could block the effects of RvD2, which is believed to occur through the GPR18-ERK1/2-NOS signalling pathway[119,120]. Conversely, MaR1 is presumed to protect against ischemic-reperfusion brain injury by increasing the expression of silent information regulator 1 (SIRT1) and Bcl2, negatively regulating acetylated kappa B (AC-NF-κB) and Bax expression, resulting in a decrease of pro-inflammatory interleukins IL-1, IL-6, and TNF-α, ultimately leading to reduced neuronal degeneration, infarct size, and neurological sequelae. These effects were partially blocked when administering the SIRT1 inhibitor EX527[121,122].

**Specialised pro-resolving lipid mediators in cns diseases: potential therapeutic targets**

Given the anti-inflammatory role of SPMs in the pathogenesis of the neurological and neurodegenerative diseases discussed earlier, inducing the resolution of inflammation represents an emerging therapeutic strategy that would present a new approach to treating and managing CNS diseases. Post-mortem studies, animal models of CNS disease, and in vitro studies have revealed that SPMs and/or their analogues exhibit anti-inflammatory effects that could reduce damage, progression, and even the onset of these pathologies (Table 1)[14].

**Table 1. Specialised lipids as therapeutic targets in CNS diseases**

| CNS Disease | Author | Methodology | Results |
|---|---|---|---|
| AD | Kantarci et al. [75] | 1-month-old mice treated with RvE1 or LXA4 alone or combined thrice a week for 2 months. | Regarding microglia and astrocyte activation, the combination of RvE1 and LXA4 was more potent than RvE1 or LXA4 alone. |
| | Mizwicki et al. [139] | AD patients and healthy controls were treated with PBMC immunomodulators: 1,25D3 and RvD1. | 1,25D3 and RvD1 improved FAM-Aβ by macrophages in AD besides inhibiting apoptosis induced by fibrillar Aβ. |
| | Yin et al. [80] | Mice received MaR1 via intracerebroventricular injection. | Treatment with MaR1 significantly improved cognitive impairment, astrocyte activation, and microglia attenuation. |
| | Wang et al. [140] | AD patients were treated with 1,7g DHA and 0,6g EPA. | A decrease in plasma levels of arachidonic acid in patients treated with DHA and EPA was evidenced. |
| | Krashia et al. [9]8 | Transgenic mice were injected with RvD1 intraperitoneally. | RvD1 prevented central and peripheral inflammation, neuronal dysfunction, and motor deficits in PD. |
| PD | Bennouna et al. [141] | Mice were fed diets supplemented with EPA and DHA. | EPA and DHA levels helped maintain the levels of plasmalogens. |
| ALS | Martínez [142] | MaR1 was administered to adult mice in the pre-symptomatic phase of ALS. | MaR1 significantly delayed the disease and its progression. |
| | Liu et al. [106] | The study was carried out in post-mortem spinal cords of ALS. | RvD1 inhibits the production of IL-6 and TNF-α in ALS macrophages. |
| Epilepsy | Frigerio et al. [112] | Male mice were administered PD1. | PD1 was found to decrease the secretion of -1β and TNF-α. |
| | Schlanger et al. [143] | Patients consumed a special diet containing 65% n-3 | A reduction in the frequency and strength of epilepsies was evidenced. |
| | Ibrahim et al. [144] | 99 patients suffering from DRE received capsules of DHA or EPA. | There was a significant decrease in seizures compared to the placebo group. |
| MS | Poisson et al. [118] | B6 mice with chronic EAE underwent metabolomics and were given RvD1 orally daily. | RvD1 reduced the progression of the disease by suppressing autoreactive T cells. |
| | Torkildsen et al. [145] | MS patients were administered n-3 for 18 months. | No major changes were evidenced between the placebo and experimental patients. |
| | Weinstock-Guttman et al. [146] | Patients were assigned to various diets; one group was low-fat (15%) with n-3 and the other was high-fat (30%). | Better outcomes were observed in patients on the low-fat diet with n-3 supplementation. |
| Stroke | Hawkins et al. [147] | Male mice were administered BML-111 intravenously after a transient occlusion of the middle cerebral artery. | Treatment with BML-111 significantly decreased the size of the infarct and vasogenic oedema. |
| | Ye et al. [148] | The efficacy of LXA4 was evaluated in rats with cerebral ischemia. | LXA4 improved neurological dysfunctions, reduced infarct volume, and attenuated neuronal apoptosis. |

**Abbreviations:** RvE1: Resolvin E1; PD: Parkinson's Disease; LXA4: Lipoxin A4; NF-kB: Nuclear factor kappa-light-chain-enhancer of activated B cells; PBMC: Peripheral Blood Mononuclear Cells; RvD1: Resolvin D1; RvD2: Resolvin D2; 125D3: 2-Vitamin D3; AD: Alzheimer's Disease; FAM-Aβ: Microglial Phagocytosis of Amyloid β Peptide; Aβ: Amyloid β Peptide; MaR1: Maresin 1; ALS: Amyotrophic Lateral Sclerosis; IL-6: Interleukin 6; TNF-α: Tumor Necrosis Factor α; NPD1: Neuroprotectin D1; DHA: Docosahexaenoic Acid; PD1: Protein D1; MS: Multiple Sclerosis; EPA: Eicosapentaenoic Acid; n-3: Omega-3 Polyunsaturated Fatty Acids; EDSS: Expanded Disability Status Scale; DRE: Drug-Resistant Epilepsy.

Regarding AD, Medeiros et al. reported that the activation induced by acetylsalicylic acid of endogenous LXA4 in mice could decrease the progression of AD, as it mediates the shift from the secretion of pro-inflammatory cytokines to anti-inflammatory profile and increases microglial Aβ phagocytosis, thus reducing synaptotoxicity and ultimately improving cognitive function[123]. Similarly, Kantarci et al. revealed that RvE1, LXA4, or a combination of both as treatment in animal models with AD reduced Aβ plaques and pro-inflammatory cytokine and chemokine levels[72]. A similar study demonstrated that RvE1 treatment enhances peripheral macrophage Aβ phagocytosis in patients with AD and also prevents fibrillar Aβ-induced apoptosis in these cells, effects previously mediated by the binding of RvE1 to the GPR32 receptor[124]. Moreover, Yin et al. studied the effect of MaR1 on pathological changes and behavioural deficits observed in AD mouse models, concluding that MaR1 treatment significantly mitigated cognitive impairment, decreased astrocyte and microglia activation, and favoured anti-inflammatory cytokines such as the production of IL-2 and IL-10[125].

In the same vein, it has been shown that administering RvD1 in subjects suffering from Parkinson's disease can prevent chronic inflammation in the CNS at both central and peripheral levels and motor deficits and neuronal dysfunction[93]. Additionally, the administration of omega-9 and supplementation with eicosapentaenoic acid and docosahexaenoic acid helped maintain stable levels of plasmalogens; also, a significant alteration of lipids in the hippocampus was demonstrated when associated with cognitive impairment in Parkinson's disease[126]. Regarding ALS, Martínez reported that the administration of MaR1 in mouse models (SOD1G93A) during the presymptomatic phase of ALS significantly delays the onset of the disease, while in those samples where treatment began in later stages, MaR1 managed to slow the progression of the disease[127]. Similarly, in a post-mortem study by Liu et al., it was demonstrated that in vitro administration of RvD1 in macrophages from ALS spinal cord samples inhibits the production of pro-inflammatory cytokines IL-6 and TNF-α while inhibiting the transcription and production of pro-inflammatory cytokines and chemokines in peripheral blood mononuclear cells[99].

On the other hand, SPMs could also represent a therapeutic alternative for other neurological disorders, such as epilepsy. In this sense, Frigerio et al. verified that the administration of PD1 in murine models of epilepsy reduced the secretion of pro-inflammatory cytokines, specifically IL-1β and TNF-α, also controls the onset of neuroinflammation and propagation during epileptogenesis and reduces the number and duration of spontaneous seizures after the onset of the disease[102]. Additionally, in a rodent model study by Musto et al., it was demonstrated that the administration of DHA, which is actively transformed into NPD1, limits electrically induced hyperexcitability in the hippocampus and that seizures also trigger the endogenous synthesis of NPD1 in the hippocampus[105]. Regarding MS, insufficient preclinical evidence supports using SPMs as potential therapeutic compounds in this pathology. However, in a study conducted by Poisson et al., it was found that daily oral administration of RvD1 in mice with MS curbs the progression of the disease by suppressing autoreactive T cells and inducing the activation of the M2 phenotype in macrophages and microglia[107].

Conversely, it has been argued that SPMs represent a therapeutic target in resolving inflammation after cerebrovascular events. For this reason, Hawkins et al. sought to demonstrate that administration for one week of BML-111, a synthetic analogue of LXA4, could have neuroprotective effects and reduce neurobehavioral deficit in rats subjected to ischemic stroke. Although the effects mentioned above were not observed, the administration of BML-111 led to an increase in the microglial cell population, a decrease in M1 CD40+ macrophages, and a decrease in the level of pro-inflammatory cytokines, resulting in a reduction in infarct size and improved sensorimotor function, one week after the occurrence of the stroke[128]. In a previous study conducted by the same research group, it was discovered that post-ischemic intravenous administration of BML-111 in rats with cerebral infarct reduces infarct size, microglial activation, neutrophil infiltration, and vasogenic oedema and also prevents disruption of the blood-brain barrier[129]. Likewise, Ye et al. reported that administration of synthetic analogue LXA4 methyl ester (LXA4 ME) immediately after the occurrence of stroke in rats significantly reduced neuronal apoptosis and infarct size, decreased neuronal dysfunction, and inhibited neutrophil infiltration, also decreasing the expression and induction of TNF-α and IL-1β, and anti-inflammatory expression of IL-10 and TGF-β1[130].

Taken together, it seems reasonable to consider how resolution pharmacology could feasibly translate to the treatment of clinical CNS disease, most importantly, systemic administration of SPMs and enhancing the endogenous synthesis of SPMs through dietary supplements of PUFA precursors (DHA and EPA)[131–133]. However, although the pharmacological safety, tolerability, and properties of a certain RvE1 analogue compound have been reported in healthy individuals[134], to date, no clinical trials have studied the direct effect of SPMs or their analogues on the typical neuroinflammation observed in patients with CNS disease. It has been widely reported that exogenous administration of PUFA increases levels of EPA and DHA in plasma and CSF[135,136]. However, clinical trials of omega-3 dietary supplementation in patients with AD so far have not yielded any significant beneficial results in preventing the onset, progression of the disease, or mitigation of AD symptoms[137,138]. At the same time, studies on MS have shown various contrasting and contradictory results[139–141]. However, some studies have confirmed the positive effect of PUFA supplementation in chronic and refractory epilepsy[142–145].

## Conclusions

Since the discovery of the first SPMs less than 20 years ago, research has focused on a small fraction of the vast array of existing pro-resolving lipid mediators. Although knowledge on the topic is limited due to its relatively recent discovery and development, it is evident that SPMs play a crucial role in actively terminating the immune response, as they can reduce inflammation and maintain tissue homeostasis. As detailed throughout, SPMs are the cornerstone of resolving neuroinflammation in each CNS disease mentioned earlier. There is sufficient epidemiological and preclinical evidence supporting the possibility of considering SPMs as potential therapeutic targets for CNS disease management.

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