Specialized Pro-Resolving Mediators in Neuroinflammation

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Specialized pro-resolving mediators (SPMs) are lipid mediators derived from poly-unsaturated fatty acids (PUFAs) which have been demonstrated to play an important role in the inflammation environment, preventing an overreaction of the organism and promoting the resolution of inflammation.

specialized pro-resolving mediators resolvins maresins annexins lipoxins protectins neuroinflammation neurodegeneration cerebrovascular disorders multiple sclerosis

1. Specialized Pro-Resolving Mediators: Metabolism, Receptors, Pathways

1.1. Overview on Specialized Pro-Resolving Mediators

Inflammation is a cascade event preserved along the evolution from the first multicellular precursor organisms to humans. Its main role is to defend tissues from an insulting agent, such as microbes or direct damage, enabling in most cases a natural return to homeostasis. If inflammation is not someway stopped, it can lead to serious consequences, such as uncontrolled edema [1].

For many years, it was assumed that inflammation was a self-limiting process [1]. However, recent discoveries have shown the presence of an active de-escalation process, promoted by a class of molecules, namely specialized pro-resolving mediators (SPMs). From the beginning of the inflammation process, SPMs reach the site of edema, either transported by blood flow or produced within the inflammatory tissue [1]. Since chronic and/or uncontrolled inflammation plays a key role in a variety of diseases (such as cardiovascular diseases, metabolic syndrome, and neurological diseases), SPMs have a potential therapeutic role. In particular, SPMs are lipid mediators (LMs) derived from PUFAs (poly-unsaturated fatty acids), such as AA (Arachidonic Acid), EPA (eicosapentaenoic acid), DHA (docosahexaenoic acid) and *n*-3 DPA (*n*-3 docosapentaenoic acid). The properties of ω-3 fish oil fatty acids in human disease and physiology may in part be explained by the formation of autacoids derived from PUFAs [1]. SPMs include lipoxins, resolvins, protectins and maresins, as well as newly identified cysteinyl-conjugated SPMs (cys-SPMs) and *n*-3 DPA-derived SPMs [2]. In the following paragraphs, each group of SPMs will be analyzed.

1.1.1. Lipoxins

Lipoxins (LX) LXA4 and LXB4 [1][3] were the first discovered SPMs. Lipoxins derive from eicosanoids thanks to a mechanism of lipo-oxygenation. Eicosanoids in turn derive from AA, an ω-6 fatty acid implied in inflammation. AA is converted into LXA4 and LXB4 via 5- lipoxygenase and 15- lipoxygenase. Lipoxins are produced by leukocytes in transcellular biosynthesis steps during interactions between leukocytes and mucosal cells or platelets [1]. Initially, Lipoxins were believed to be agents of anti-inflammation, and their pro-resolution role has only recently been discovered. Aspirin can trigger their biosynthesis thanks to its capacity to promote the formation of LMs via lipo-oxygenation [4].

1.1.2. Resolvins

Resolvins are generated in inflammatory exudates during the phase of resolution. They derive from ω-3 fatty acids EPA and DHA, forming E series (RvE) and D series (RvD) resolvins, respectively. Their synthesis is also promoted by aspirin (likewise Lipoxins) [1]. Resolvins act in several ways in order to interrupt the inflammation cascade. In particular, they [1]:

- inhibit the production of pro-inflammatory mediators, such as chemokines and cytokines
- enhance scavenging of pro-inflammatory chemokines
- promote the recruitment of monocytes and phagocytes' clearance via the lymphatic system
- limit PMN (polymorphonuclear cells) migration and infiltration
- Focusing on the subclass of Resolvins, it can be found [2]:
- E-series Resolvins: RvE1, RvE2, RvE3 and the recent RvE4;
- D-series Resolvins: RvD1, 17R-ResolvinD1, RvD2, RvD3 and 17R-Resolvin D3, RvD4, RvD5.

1.1.3. Protectins

Protectins consist of Protectin D1/Neuroprotectin D1 (PD1/NPD1). They are biosynthesized from DHA via the 15-LOX mechanism. It can be found in human cell types, murine exudates and brain tissue; in this last case, it is called "NeuroprotectinD1" (NPD1), whereas PD1 operates in peripheral tissue. PD1/NPD1 has neuroprotective properties in the brain, retina and Central Nervous System (CNS). Its aspirin-triggered epimer, 17R-NPD1, has the same actions as NPD1 in controlling PMN, enhancing macrophage functions and attenuating experimental stroke [2].

1.1.4. Maresins

Maresins were first identified in human macrophages, in a pathway initiated by 12-LOX. Their name derives from an acronym: Macrophage Mediators in Resolving Inflammation. Maresin1 (MaR1) is able to promote the

regeneration of tissues in an experimental model of simple organisms (planaria) with a strong capability of regeneration. In human cells, it is produced by platelets and PMN interactions. MaR1 promotes tissue regeneration and repair and has a neuroprotective role [2].

1.1.5. Recently Discovered SPMs

Recently discovered peptide-lipid conjugated SPMs include cysteinyl-SPMs (cys-SPMs). They consist of three series of SPMs, each one with three bioactive members: maresin conjugates in tissue regeneration (MCTR), protectin conjugates in tissue regeneration (PCTR) and resolving conjugates in tissue regeneration (RCTR). They show pro-repair and pro-regenerative actions [2]. For the sake of completeness, it is important to mention n3-DPA-derived SMPs: RvDn-3 DPA, MaRn-3 DPA and PDn-3 DPA, 13-series resolvins (RvTs). They share the potent actions of DPA and EHA-derived SPMs in the resolution of systemic inflammation and neuro-inflammation. RvTs' biosynthesis is promoted by atorvastatin via S-nitrosylation of cyclooxygenase-2 (COX-2) [2].

1.2. Receptors and Pathways

It is important to emphasize that these endogenous mediators of resolution do not act thanks to an "inhibition" of inflammation pathways: instead, they actively promote specific pathways in order to obtain a return to homeostasis. There are specific G-protein-coupled seven-transmembrane receptors (GPCR) activated by SPMs [1]. Every single class of SPM demonstrates stereoselective activation of its own GPCR. SPMs show affinities for ligand-receptors in the nano-picomolar range, thus demonstrating a potent action in vitro and in vivo [2].

Resolvin E1 (RvE1) acts via ChemR23 (GPCR for RvE1). It is also a partial agonist on the LTB_4 (leukotriene B4) receptor (BLT1), activated by LTB_4 as well. Nevertheless, RvE1 has a different mechanism of action, which is a time and dose-dependent phosphorylation of Akt and p70S6K (ribosomal protein S6 kinase) via ChemR23 [1].

Resolvin D1 (RvD1) binds two separate GPCR on human leukocytes: ALX/FPR2 (LXA_4 receptor) and GPR32 (GPCR for RvD1) [1]. ALX/FPR2 receptors can also be activated by Annexin-1 and Chemerin [5]. Deficits in ALX/FPR2 in experimental models (mice) amplify cardiomyopathy, age-related obesity, and leukocyte-directed endothelial dysfunction [6].

MaR1 can activate two classes of receptors:

- leucine-rich repeat-containing G protein-coupled receptor 6 (LGR6), a phagocyte's receptor
- retinoic acid-related orphan receptor α (ROR-α), a liver macrophages' nuclear receptor

Stimulating the LGR6 receptor, MaR1 can promote phagocytosis, efferocytosis, and the phosphorylation of select proteins [7]. NPD1/PD1's receptor, GPR37, increases intracellular Ca^{2+} in macrophages and promotes phagocytosis [8]. RvD5n-3 DPA binds an orphan receptor, GPR101, with high stereospecificity [2]; in experimental KO models of GPR101, there is a lack of protective action of RvD5n-3 in inflammatory arthritis [9].

These receptors demonstrate overlapping actions (for example, ALX, GPR18, LGR6 and GPR101 can promote calcium mobilization via cAMP signal) and distinct actions too; thus, they could act in tandem to promote defense from injury, inflammation, and infection [2].

1.3. Mechanism of Action

The first signs of inflammation response are vasodilation and changes in vessel permeability. These factors not only permit the recruitment of cells implied in the inflammatory response but also give substrates for the biosynthesis of important molecules, such as SPMs [1]. Apparently, ω-3 PUFAs, AA, EPA and DHA can be found within inflammatory exudates during very early phases, as demonstrated in various works [10][11]. Therefore, the inflammation response is counterbalanced early by pro-resolution mediators. This avoids an excess of an inflammatory response that can be disruptive for the organism and for the tissue itself [1].

2. Specialized Pro-Resolving Mediators and Neuroinflammation

2.1. Neuroinflammation and Its Resolution

While inflammation is usually a self-limiting physiological process, when persistent or dysregulated it can become harmful to human tissues; if this happens within the CNS it is referred to as neuroinflammation and many studies proved that chronic neuroinflammation could ultimately lead to neurodegeneration [12][13][14]. In this picture, an emerging concept is the resolution of neuroinflammation which contributes to brain homeostasis; a great deal of attention has been paid to the topic in the last few years. The main actors of this specular process are the so-called SPMs, whose characteristics have been explained in the previous chapter. In the last decade, several research groups started to investigate the role of SPMs in the nervous tissue as regulators of the inflammation process that may contribute to the crosstalk between glial cells and neurons in several neurological pathologies [15].

2.2. The Role of Glial Cells in Neuroinflammation and the Contribution of SPMs

Nervous tissue is composed of about 100 billion neurons and 80 to 100 billion glial cells, namely ectoderm-derived astrocytes and oligodendrocytes, and mesoderm-derived microglial cells. Astrocytes play a key role in the metabolism and metabolic support of nervous parenchyma and specifically neurons, i.e., lactate shuttle, the glutamate–glutamine cycle, and ketone bodies supply. Neuroinflammation has lately been interpreted as a condition of metabolic imbalance and energetic depletion, both in the acute and chronic settings. It hence derives that glial cells play a crucial role in the control of neuroinflammation, by regulating nervous tissue metabolism.

As demonstrated, brain tissue contains high levels of PUFAs, mainly DHA and AA, which are the principal precursors of SPMs. The main PUFA source is unesterified plasma fatty acid pool rather than endogenous synthesis; such a source is severely impacted by dietary supply according to studies conducted on rodents [16][17]. Interestingly, the hippocampus and prefrontal cortex contain the highest DHA content while the hypothalamus has

the lowest [15]. As for their proportion of representation in the human brain, astrocytes contain 10–12% of DHA, oligodendrocytes 5%, and microglial cells up to 2% [18]. Astrocytes, the most abundant glial cells present in the nervous tissue, take part in many vital processes, such as the migration of developing axons and certain neuroblasts, the regulation of blood flow, electrolyte homeostasis, blood–brain barrier (BBB), and synapse function. Moreover, they seem to be the main glial cells involved in neuroinflammation, although they show significant diversity in this process. For instance, they express high levels of the ALX/FPR2 receptor, which has a central role in the regulation of astrogliosis, an active inflammatory path that leads to neural protection, repair and ultimately to glial scarring [15]. LXA_4 and RvD1, the two SPMs that bind this receptor, promote the inhibition of astrocytes' pro-inflammatory activities [19]. Moreover, it has been observed that peripheral RvD1 administration in brain injury models improved its functional recovery through an ALX/FPR2-regulated pathway probably induced by astrocytes [15]. Another important receptor expressed by astrocytes and playing an important role in neuroprotection is ChemR23/ERV1, expressed in the human hippocampus, which binds RvE1: animal studies demonstrated that peripheral administration of RvE1 in Alzheimer's disease (AD), in combination with LXA_4, reduced astrocyte activation [20]. Other receptors involved in the neuroprotection and resolution of inflammation are GPR37, GPR18 and LgR6, whose expression in astrocytes is challenged, and further studies both in vivo and in vitro are needed on this subset. Besides their main function of myelin synthesis, oligodendrocytes, the second most represented cell population in the CNS, may play a role in the resolution of neuroinflammation thanks to the latest evidence on their active production of immune-regulatory factors or their receptors [21]. Comparing oligodendrocytes with astrocytes, ALX/FPR2 is not expressed by these cells; the only SPMs receptor identified seems to be GPR37 [22]. On the other hand, microglia, the immune cells of the CNS, thanks to their very physiological role, seem to express all the known SPM receptors and are susceptible to the effects of different SPMs categories (lipoxins, RvE, RvD, protectins and maresins) [15][23]. Nonetheless, the cellular origin of SPMs in these cells, as in astrocytes and oligodendrocytes, has not yet been demonstrated and only a few in vitro studies have tried to investigate it [16].

3. Specialized Pro-Resolving Mediators and Potential Applications in Neuroinflammatory Conditions

3.1. Specialized Pro-Resolving Mediators in Ischemic Stroke and Cerebrovascular Events

The concept of ischemic stroke has been expanded to include not only what happens inside the vessel, but also in the surrounding environment, the so-called "neurovascular unit", which includes the interaction between glia, neurons, vascular cells, and matrix components; after the acute event, secondary neuroinflammation takes place, bringing about detrimental effects producing further injury and neuronal death, and promotion of recovery [24]. Several studies have investigated the possible role of pro-resolving mediators in improving post-stroke prognosis; however, they have mostly been conducted on rodents, and applications in humans remain speculative and in need of further research. **Table 1** provides a summary of in vivo studies on SPMs in ischemic stroke and cerebrovascular events.

Table 1. Summary of in vivo studies on SPMs in ischemic stroke and cerebrovascular events.

Reference	Type of Study	Animal Model	Pro-Resolving Mediator	Delivery (Or Measurement If the Study Was Non-Interventional)	Outcome
Zuo et al., 2018 [25]	Animal study	MCAO mouse model	RvD2	intraperitoneal	↓ infarction, inflammation, edema, and neurological dysfunction; compared with ω-3 fatty acid oral supplements, better rescue effect on cerebral infarction
Dong et al., 2019 [26]	Animal study	MCAO mouse model	RvD2	Intravenous infusion of RvD2-loaded nanovesicles	↓ inflammation; ↑ neurological function
Fredman et al., 2016 [27]	Animal study	fat-fed Ldlr-/- mice	RvD1	Immunoprecipitation injection	↓ atherosclerosis
Kotlęga et al., 2021 [28]	Human study	-	RvD1	blood levels of endogenous pro-resolving mediators	Post-stroke blood levels of RvD1 correlated with a better cognitive performance
Xian et al., 2016 [29]	Animal study	MCAO mouse model	MaR1	Intracerebroventricular	↓infarct volume and neurological defects by inhibiting NF-kB p65 function
Xian et al., 2019 [30]	Animal study	MCAO mouse model	MaR1	Intracerebroventricular	↓ inflammation and mitochondrial damage via activation of SIRT1 signaling
Vital et al., 2020 [31]	Animal study	Lipopolysaccharide and sickle transgenic mice models of thrombo-inflammation	AnxA1 mimetic peptide Ac2-26	Intravenous	↓ thrombo-inflammation via Fpr2/ALX receptor and ↓ platelet aggregation
Gavins et al., 2007 [32]	Animal study	MCAO in wild-type or AnxA1−/− mice	AnxA1 mimetic peptide Ac2-26	Intravenous	↓ inflammation via receptors of the FPR family

Reference	Type of Study	Animal Model	Pro-Resolving Mediator	Delivery (Or Measurement If the Study Was Non-Interventional)	Outcome
Xu et al., 2021 [33]	Animal study	MCAO mouse model	AnxA1 mimetic peptide Ac2-26	Intravenous	↓ inflammation by regulating the FPR2/ALX-dependent AMPK-mTOR pathway
Ding et al., 2020 [34]	Animal study	Collagenase-induced ICH mouse model	Recombinant human AnXA1	Intracerebroventricular	↓ inflammation via the FPR2/p38/COX-2 pathway
Senchenkova et al., 2019 [35]	Animal study	MCAO in wild-type or AnxA1−/− mice	Whole protein AnXA1	Intravenous	↓ platelet aggregation by affecting integrin (αIIbβ3) activation
Li et al., 2021 [36]	Animal study	MCAO mouse model	LXA4	Intracerebroventricular	↓ proinflammatory cytokines and regulate microglial M1/M2 polarization via the Notch signaling pathway
Wu et al., 2013 [37]	Animal study	MCAO mouse model	LXA4	Intracerebroventricular	↓infarct volume and ↑ neurological function through Nrf2 upregulation
Hawkins et al., 2014 [38]	Animal study	MCAO mouse model	LXA4 analog BML-111	Intravenous	↓ infarct size, edema, BBB disruption, and hemorrhagic transformation
Hawkins et al., 2017 [39]	Animal study	MCAO mouse model	LXA4 analog BML-111	Intravenous	↓ infarct volume; and ↑ neurological function at 1 week. No reduction of infarct size or improvement of behavioral deficits 4 weeks after ischemic stroke
Wu et al., 2010 [40]	Animal study	MCAO mouse model	LXA4 ME	Intracerebroventricular	↓ proinflammatory cytokines, neurological dysfunctions,

Reference	Type of Study	Animal Model	Pro-Resolving Mediator	Delivery (Or Measurement If the Study Was Non-Interventional)	Outcome
					infarction volume, and neuronal apoptosis
Ye et al., 2010 [41]	Animal study	MCAO mouse model	LXA4 ME	Intracerebroventricular	↓ proinflammatory cytokines, neurological dysfunctions, infarction volume, and neuronal apoptosis
Wu et al., 2012 [42]	Animal study	MCAO mouse model	LXA4 ME	Intracerebroventricular	↓ BBB dysfunction and MMP-9 expression; ↑ TIMP-1 expression
Jin et al., 2014 [43]	Animal study	BCCAO	LXA4 ME	Intracerebroventricular	Amelioration of cognitive impairment via ↓oxidative injury and ↓neuronal apoptosis in the hippocampus with the activation of the ERK/Nrf2 signaling pathway
Wang et al., 2021 [44]	Human study	-	LXA4, RvD1, RvD2, RvE1, MaR1	blood levels of endogenous pro-resolving mediators	↓ LXA4 in patients with post-stroke cognitive impairment
Guo et al., 2016 [45]	Animal study	endovascular perforation model of SAH	Exogenous LXA4	Intracerebroventricular	↓ neuroinflammation by activating FPR2 and inhibiting p38
Liu et al., 2019 [46]	Animal study	endovascular perforation model of SAH	Recombinant LXA4	Intracerebroventricular	↓ endothelial dysfunction and neutrophil infiltration, possibly involving the LXA4/FPR2/ERK1/2 pathway
Yao et al., 2013 [47]	Animal study	MCAO mouse model	NPD1	Intracerebroventricular	↓ infarct volume and ↑ neurological

Reference	Type of Study	Animal Model	Pro-Resolving Mediator	Delivery (Or Measurement If the Study Was Non-Interventional)	Outcome
					scores through inhibition of calpain-mediated TRPC6 proteolysis and activation of CREB via the Ras/MEK/ERK pathway
Eady et al., 2012 [48]	Animal study	MCAO mouse model	NPD1	Intravenous	↓ infarct size in aged rats via activation of Akt and p70S6K pathways
Belayev et al., 2017 [49]	Animal study	MCAO mouse model	DHA (NPD1 precursor)	Intravenous	↓ oxidative stress by upregulating ring finger protein 146 (Iduna) in neurons and astrocyte
Zirpoli et al., 2021 [50]	Animal study [53]	Unilateral cerebral hypoxia-ischemia injury mouse model	NPD1	Intraperitoneal	↓ ischemic core expansion, preserved mitochondrial structure and ↓ BAX translocation and activation
Belayev et	Animal	MCAO mouse			↑ neurogenesis and angiogenesis, BBB integrity, and long-

Reference.	Type of study	Model	Pro-resolving mediator	Delivery (or measurement if the study was non-interventional)	Outcome
Paschalidis N et al., 2009[54]	Animal study	MOG34-55 - induced EAE in AnxA1 null mice compared to MOG34-55 - induced EAE in control mice	Absence of AnxA1 expression	Measurement of disease activity in spinal cord; lymph-node cells (respectively, by isolation of T-cells and/or fixation with haematoxylin and eosin; and by test	↓ signs of the disease in AnxA1 null mice compared to wild type mice ↓ infiltration of T cells in the spinal cord of AnxA1 null mice compared to wild type

				ELISA for Th1/Th17 cytokine profile)	
Huitinga I et al., 1998 [55]	Animal study	EAE rats (MS mouse model)	AnxA1	Intracerebroventricular administration	↓ neurological severity
Poisson LM, 2015 [56]	Animal study	EAE rats (MS mouse model)	RvD1	Oral administration	Attenuation of disease progression by suppressing autoreactive T cells and inducing an M2 phenotype of monocytes/macrophages and resident brain microglial cells
Derada Troletti C et al., 2021 [57]	Animal study	EAE rats (MS mouse model)	LXA4	Intraperitoneal injection	Improvement of EAE clinical symptoms and inhibit CD4+ and CD8+ T cell infiltration into the CNS
Derada Troletti C et al., 2021 [57]	*In vivo* and in vitro study	Human T cells from healthy donors and patients with relapsing-remitting MS	LXA4	Measurement of T-cell functions	↓ encephalitogenic Th1 and Th17 effector functions
Sánchez-Fernández A et al., 2022 [58]	Animal study	EAE rats (MS mouse model)	MaR1	Intraperitoneal injection	Suppression of various pro-inflammatory cytokines, ↓ number of Th1 cells

					↑ of Tregs polarization of macrophages towards an anti-inflammatory phenotype
Prüss H et al., 2013 [59]	Human study	MS patients	RvD1 NDP1	CSF levels	↑ of RvD1 Only detection of NDP1
Kooij G et al., 2020 [60]	Human study	NMOSD patients	RvD1 LTB4	CSF levels	RvD1 ↓ LTB4 ↑
Luo B et al., 2016 [61]	Animal study	EAN (experimental autoimmune neuritis) model	RvD1	Intraperitoneal injection	Macrophage phagocytosis of apoptotic T cells in PNS, ↑ TGFβ by macrophages, ↑ local Treg cell counts, and promotion of inflammation resolution and disease recovery

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all, a shift
in the LM profile in the CSF from pro-resolving to pro-inflammatory occurs as AD progresses. In a recent study, liquid chromatography–tandem mass spectrometry was used to analyze pro-resolving and pro-inflammatory LMs in the CSF of patients with cognitive impairment ranging from subjective impairment to a diagnosis of AD; LMs profile correlated to cognition, CSF tau, and β-amyloid. RvD4, RvD1, NPD1, MaR1, and RvE4 were lower in AD and/or mild cognitive impairment (MCI) compared to subjective cognitive impairment (SCI); on the other hand, pro-inflammatory mediators were higher in AD and MCI [63]. Similarly, it was found that the levels of the MaR1, NPD1 and RvD5, were lower in the entorhinal cortex of AD patients as compared to age-matched controls, while levels of the pro-inflammatory prostaglandin D2 (PGD2) were higher in AD [64]. In addition, RvD4 showed a negative correlation to AD tangle biomarkers and positive correlations to cognitive test scores [63]. Similar findings have been reported in mice, where SPMs in the brain cortex were substantially lower in mice with an APOE4 genotype [65]. The finding that SPMs receptors are increased in the AD brain in post-mortem studies and correlate to Braak stages, suggests a prominent role of resolution pathways; the increase in these receptors may either represent a primary factor in the pathogenesis of the disease or a consequence of failed resolution [66]. The same study group investigated age-related changes in the LM profile in the APP knock-in (APP KI) mouse model of AD, concluding

* AnXA1: Annexin A1; AT-NPD1: aspirin-triggered NPD1; BCCAO: bilateral common carotid artery occlusion; DHA: docosahexaenoic acid; EAE: Experimental Autoimmune Encephalitis; EAN: Experimental Autoimmune Neuritis; FPR: formyl-peptide receptor; LXA4: Lipoxin A4; LXA4 ME: Lipoxin A4 Methyl Ester; LTB4: Leukotriene B4; MaR1: Maresin1; NPD1: Neuroprotectin D1; PNS: peripheral nervous system; RvD1: Resolvin D1.

that the brain lipidome appeared to be modified preferentially during aging as compared to amyloid pathology, as the oldest age group was the one with the greatest increase in LMs, despite an early onset of Aβ pathology [67]. In this case, the SPMs biosynthetic enzymes were found to be increased, while their receptor expression decreased in the aged App KI mice, in disagreement with their previous work [66] on AD patients. The discrepancy may be explained by the fact that the stage of AD pathology in 18-month-old App KI mice is likely less advanced compared to that seen in human post-mortem brains [67]. Several in vivo mouse studies support the potential benefit deriving from SPM use in AD. **Table 3** provides a summary of in vivo studies on SPMs in neurodegenerative diseases.

Table 3. Summary of in vivo studies on SPMs in neurodegenerative diseases.

Reference	Type of study	model	Pro-resolving mediator	Delivery (or *measurement if the study was non-interventional*)	Outcome
Do K V et al., 2022 [68]	Human, non-interventional	Patients with AD, MCI, SCI	RvD4	*CSF levels of RvD4*	Negative correlation to AD tangle biomarkers, and positive correlations to cognitive test scores
Zhu M. et al., 2016 [69]	Human study	Patients with AD	MaR1, NPD1, RvD5	*Postmortem tissue samples from the entorhinal cortex*	↓ concentration of pro-resolving mediators in the entorhinal cortex of AD patients as compared to age-matched controls, while levels of the pro-inflammatory prostaglandin D2 were higher in AD
Martinsen A. et al.,	Animal study	APOE4 Female mice	Various SPMs	*Brain postmortem tissue samples*	↓ SPMs in mice with the APOE4

2019 [70]					genotype
Emre C. et al., 2020 [71]	Human study	Patients with AD	SPMs receptors	*Brain postmortem tissue samples*	↑ SPMs receptors
Emre C, Do K V. et al., 2021 [67]	Animal study	APP KI mouse model of AD	LMs profile	*Brain postmortem tissue samples*	↑ microglia proliferation starting from a young age in the App KI mice, while ↓ astrocyte numbers in older ages Brain lipidome appears to be modified preferentially during aging as compared to amyloid pathology, as the oldest age group was the one with the greatest increase in LMs, despite an early onset of Aβ pathology
Emre C, Arroyo-García et al., 2022 [72]	Animal study	Murine model of AD	RvE1, RvD1, RvD2, MaR1 and NPD1	Intranasal	Amelioration of memory deficits; restoration of Gamma oscillation deficits; ↓ microglial activation

Kantarci A. et al., 2017 [20]	Animal study	Murine model of AD	RvE1 and LXA4	Intraperitoneal	↑ RvE1, LXA4, and RvD2 in the hippocampus; reversing of the inflammatory process, ↓ neuroinflammation
Wu J. *et al., 2011* [73]	Animal study	Murine model of AD	LXA4	Intracerebroventricular	Inhibiting the inflammatory response induced by β-amyloid in the cortex and hippocampus (in particular, production of IL-1b and TNFa)
Serhan CN., 2005 [74]	Animal study	Murine model of AD	ATL	Subcutaneous	↓ NF-kB activation and levels of proinflammatory cytokines and chemokines; creating an anti-inflammatory cerebral milieu, resulting in the recruitment of microglia in an alternative phenotype
Medeiros R. et al., 2013 [75]	Animal study	Murine model of AD	ATL	Subcutaneous	↓ phosphorylated-tau (p-tau)

Yin P. et al., 2019 [76]	Animal study	Murine model of AD	MaR1	Intracerebroventricular	Improving cognitive decline of experimental mice: attenuating microglial activation, ↓ the pro-inflammatory cytokines in favor of anti-inflammatory ones, and ↑ the levels of proteins related to survival pathway including PI3K/AKT, ERK; ↓ levels of proteins associated with inflammation, autophagy, and apoptosis pathways, such as p38, mTOR and caspase 3
Schröder N et al., 2020 [77]	Animal study	Murine model of AD	Ac2-26	Intraperitoneal injection	No beneficial effect
Park JC et al., 2017 [78]	In vitro and in vivo (animal study)	Aβ-42 treated murine brain endothelial cell line bEnd.3; Murine model of AD	Human recombinant ANXA1; ANXA1	Administration of human recombinant ANXA1 in Aβ-42 treated murine brain endothelial cell line bEnd.3; *ANXA1 levels on blood of murine model of AD*	rescuing β-amyloid 1–42 -induced BBB disruption via inhibition of RhoA-ROCK signaling pathway in brain

					endothelial cell line bEnd.3; ↓ ANXA1 in a murine model of AD
Ries M. et al., 2021 [79]	Animal study	Murine model of AD	Human recombinant AnxA1	Intravenous injection	↓ β-amyloid load and p-tau build-up in 5xFAD mice and Tau-P301L mice; prolonged treatment reduced the memory deficits and increased synaptic density in young 5xFAD mice
Tian Y. et al., 2015 [80]	Animal study	Rat model of PD	RvD2	Intrathecal injection on substantia nigra pars compacta	recovering neural injury by suppressing inflammatory mediator expression
Krashia P. et al., 2019 [81]	Animal study	Rats overexpressing human α-synuclein (Syn)	RvD1	Chronic intraperitoneal injection	preventing central and peripheral inflammation, as well as neuronal dysfunction and motor deficits

* AD: Alzheimer Disease; Aβ1-26: amyloid β peptide 1–26; ATL: Aspirin-triggered lipoxin A4; LMs: Lipid Mediators; MaR1: Maresin 1; NPD1: Neuroprotectin D1; PD: Parkinson Disease; RvD1: Resolvin D1; RvD4: Resolvin D4; RvD5: Resolvin D5; RvE1: Resolvin E1; SCI: Subjective cognitive impairment.

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