OCL 2016, 23(1) D104
© C. Joffre *et al.*, Published by EDP Sciences 2015
DOI: 10.1051/ocl/2015062

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Research Article – Dossier Open Access

Lipids and brain
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DOSSIER

Role of n-3 PUFAs in inflammation *via* resolvin biosynthesis

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Received 9 December 2015 – Accepted 2 November 2015

Abstract – The role of n-3 PUFAs has gained more importance these last decades, especially in inflammatory processes because they can display anti-inflammatory properties. Inflammation is a protective response of the body in controlling infection and promoting tissue repair. However, excessive inflammation can cause local tissue damage. This is especially the case for the brain for which the functional consequences of neuroinflammation include alterations in cognition, affect and behavior leading to a negative impact on the quality of life and well-being of patients (Dantzer, 2001, 2008). Hence, limiting the inflammation in the brain is a real strategy for neuroinflammatory disease therapy and treatment. Recent data show that n-3 PUFAs exert anti-inflammatory properties in part through the synthesis of specialized pro-resolving mediators such as resolvins that actively turned off the inflammatory response. This review first outlines basic concepts of neuroinflammation and the role of n-3 PUFAs in this process and then summarizes the biosynthesis, signaling pathways and role of resolvins.

Keywords: Microglial cells / n-3 PUFAs / RvD1 / RvE1 / neuroinflammation

Résumé – Rôle des AGPI n-3 dans les processes inflammatoires *via* la synthèse des résolvines. Le rôle des AGPI n-3 a considérablement augmenté ces dernières années, en particulier dans les processus inflammatoires en raison de leurs propriétés anti-inflammatoires. L'inflammation est une réponse protectrice de l'organisme visant à contrôler l'infection et à favoriser la réparation des tissus. Cependant, une inflammation excessive peut avoir de graves conséquences au niveau des tissus. C'est notamment le cas pour le cerveau pour lequel les conséquences fonctionnelles de la neuro-inflammation comprennent des altérations de la cognition, de l'affect et du comportement, conduisant à un impact négatif sur la qualité de vie et le bien-être des patients (Dantzer, 2001, 2008). Par conséquent, limiter l'inflammation dans le cerveau représente une véritable stratégie dans le cadre de la prévention et du traitement des maladies neuro-inflammatoires. Des données récentes montrent que les AGPI n-3 exercent leurs propriétés anti-inflammatoires en partie via la synthèse de médiateurs lipidiques spécialisés tels que les résolvines, qui participent activement à réduire la réponse inflammatoire. Cette revue rappelle d'abord les concepts de base de la réponse inflammatoire et le rôle des AGPI n-3 dans ce processus et présente ensuite la biosynthèse, les voies de signalisation et le rôle des résolvines.

Mots clés : AGPI n-3 / neuro-inflammation / résolvines / cellules microgliales

1 Introduction

The role of essential nutrients in the brain development and neuronal functioning has increased in the last decades. In this regard, polyunsaturated fatty acids (PUFAs), especially n-3 PUFAs have gained importance. They are significant structural components of the phospholipid membranes of brain in which docosahexaenoic acid (DHA; 22:6 n-3) constitutes up to 30% of total fatty acids. They assure the correct environment for membrane protein function, maintain the fluidity and influence lipid raft formation (Calder, 2010). They also act as signaling molecules or ligands for transcription factors (Norheim *et al.*, 2012). Moreover, they are involved in the cerebral development and in the neuronal structure (Madore *et al.*, 2014). They have the ability to modulate the neurotransmission and the synaptic plasticity (Lafourcade *et al.*, 2011). Of importance in many neurodegenerative diseases, they have immune-regulatory properties (Bazinet and Laye, 2014). One of the possible mechanisms to explain the n-3 PUFAs benefits has recently emerged as their conversion in bioactive lipid mediators

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such as resolvins. In this review we present an overview of the formation and action of n-3 PUFAs derived anti-inflammatory lipid mediator resolvins.

2 Neuroinflammation

Neuroinflammation is a common early feature of most peripheral and central diseases. It is characterized by the brain synthesis and release of pro-inflammatory mediators known to control neuronal function (Cunningham and Sanderson, 2008; Delpech *et al.*, 2015b; Hanisch and Kettenmann, 2007; Pascual *et al.*, 2012; Yirmiya and Goshen, 2011). Pro-inflammatory factors including interleukin-1 beta (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor alpha (TNF-α) have been directly linked to impaired neuronal plasticity in various animal models (Delpech *et al.*, 2015b; Yirmiya and Goshen, 2011).

Microglia are the resident macrophages of the brain, and constitute the first line of immune defense (Ransohoff and Cardona, 2010). They derive from myeloid cells in the periphery and comprise approximately 15% of the cells in the brain (Carson *et al.*, 2006). They are involved in tissue homeostasis control, response to injury and remodeling/repair. Under normal conditions, they are in a surveillance phenotype and constantly monitor the environment (Davalos *et al.*, 2005; Nimmerjahn *et al.*, 2005). Once stimulated by an immune challenge, microglia are capable of acquiring diverse and complex phenotypes as well as performing several macrophage-like functions including inflammatory and anti-inflammatory cytokine production (Biber *et al.*, 2007; Garden and Moller, 2006; Madore *et al.*, 2013). If sustained, microglia activation can aggravate the related injury, leading to neuronal damage that is the basis of a large variety of pathologies (Blais and Rivest, 2003; Laye, 2010; Solito and Sastre, 2012; Woodroofe, 1995; Woodroofe and Cuzner, 1993).

Hence, the identification of mediators limiting the inflammation and/or involved in the resolution of inflammation is of growing interest as it may provide novel targets in brain damage prevention and treatment.

3 Role of n-3 PUFAs in inflammation

n-3 PUFAs have been shown to have powerful immunomodulatory effects (Calder, 2001; Labrousse *et al.*, 2012; Laye, 2010; Orr *et al.*, 2013). They are highly concentrated in the central nervous system (CNS) and are necessary for normal brain development and function (Labrousse *et al.*, 2012; Larrieu *et al.*, 2012; Luchtman and Song, 2013; Moranis *et al.*, 2012; Xiao *et al.*, 2005). The dramatic reduction in the dietary supply of n-3 PUFAs in Western societies and the corresponding increase in n-6 PUFAs lead to an imbalanced n-6/n-3 ratio currently estimated at 12–20 in developed countries instead of the recommended ratio of 5 (Simopoulos, 2001). These changes in n-3 PUFAs in the diet lead to modifications in the n-3 PUFA content in the brain. As a result, we have previously demonstrated that low dietary intake of n-3 PUFAs promotes neuroinflammatory responses through the regulation of microglial cell activity and polarization toward a pro-inflammatory phenotype, whereas n-3 PUFA dietary supplementation is rather anti- inflammatory (Delpech *et al.*, 2015c; De Smedt-Peyrusse *et al.*, 2008; Labrousse *et al.*, 2012; Madore *et al.*, 2014; Mingam *et al.*, 2008). Moreover, the central n-3 PUFA increase observed in transgenic Fat-1 mice modulates the brain innate immune system activity, leading to the protection of animals against LPS-induced pro-inflammatory cytokine production and subsequent spatial memory alteration (Delpech *et al.*, 2015a). Hence, a dramatic reduction in the dietary supply of n-3 PUFAs could thus contribute to the sensitization of the brain immune response to further inflammation, and thus to the development of spatial memory disorders.

The mechanisms by which n-3 PUFAs exert their effect are not clearly established. Interestingly, their effect can be mediated *via* lipid mediators because n-3 PUFAs can act as precursors of specialized pro-resolving mediators (SPM) involved in the anti-inflammation and pro-resolution. The resolution of inflammation is an actively regulated part of the inflammatory response involving the activation of specific molecules and cells that signal the end of inflammation and turn it off.

4 Role of resolvins in inflammation

Recent data emphasize the importance of SPM generated from PUFAs. These compounds are key regulators and mediators of inflammation. They were identified using a lipidometabolomic system approach to analyze the cellular and molecular components of exudates during inflammation. They are active at nanomolar range unlike their precursors that act at micromolar concentrations (Claria *et al.*, 2011). They act locally and may be rapidly inactivated by further metabolism *via* enzymatic pathways (Arita *et al.*, 2005; Seki *et al.*, 2009). They have the ability to regulate the progress of inflammatory response and activate the resolution of inflammation in a number of cell types and models of inflammation. To date, only a few DHA-derived mediators, including 17S-hydroxy-DHA (17-HDHA), neuroprotectin D1 (NPD1), resolvin D5 (RvD5), 14-HDHA and maresin 1 (MaR1), have been identified within brain tissue (Orr *et al.*, 2013; Serhan, 2014). In patients, RvD1 was measured in plasma and macrophages (Fiala *et al.*, 2015; Wang *et al.*, 2015a). As resolvins have been mostly studied on peripheral cells, we focused on these compounds.

4.1 Biosynthesis of resolvins and receptors

Resolvins are endogenous lipid mediators derived from DHA and EPA with both anti- inflammatory and pro-resolutive activities without immune suppression (Serhan, 2008, 2014; Serhan *et al.*, 2002). Among the resolvins, resolvin D1 (RvD1, 7S,8R,17S-trihydroxy- 4Z,9E,11E,13Z,15E,19Z-docosahexaenoic acid) and resolvin E1 (RvE1, 5S,12R,18R-trihydroxy-6Z,8E,10E,14Z,16E-eicosapentaenoic acid) are of particular interest in the resolution of inflammation as they actively turn off the inflammatory response (Bazinet and Laye, 2014; Calder, 2013; Fredman and Serhan, 2011; Headland and Norling, 2015; Serhan and Chiang, 2013). Resolvins are biosynthesized through a lipoxygenase (LOX) mechanism

or by aspirin-triggered cyclo-oxygenase-2 (COX-2) pathway. RvD1 is synthesized by 15- and 5-LOX from DHA. DHA is initially converted by 15-LOX to 17S-hydroxy-DHA (17S-HDHA). Then, 5-LOX catalyzes oxygenation at carbon C7 and subsequent formation and hydrolysis of an intermediate epoxide gives rise to RvD1. This molecule acts through the binding to its receptors orphan receptor G protein coupling receptor 32 (GPR32) and lipoxin A4 receptor/formyl peptide receptor 2 (ALX/fpr2) (Krishnamoorthy *et al.*, 2010). Unlike ALX/fpr2 expressed on mouse neurons (Pei *et al.*, 2011), GPR32 has not been identified in mice. RvE1 is derived from EPA by oxygenation by aspirin-triggered acetylated COX-2 (COX-2) or cytochrome P450 enzymes and 5-LOX (Arita *et al.*, 2005; Serhan *et al.*, 2000). COX-2 or cytochrome P450 catalyzes the biosynthesis of 18R-hydroxyeicosapentaenoic acid (18R-HEPE). Then, by interaction with the 5-LOX, this intermediate is converted to RvE1. RvE1 binds two G protein-coupled receptors, chemokine-like receptor 1 (ChemR23 or CMKLR1) (Samson *et al.*, 1998) or leukotriene B4 receptor (BLT1) (Arita *et al.*, 2007). ChemR23 is expressed on monocytes, macrophages and microglia (Arita *et al.*, 2005; Ji *et al.*, 2011). BLT1 is expressed on monocytes and neutrophils but there is no study about the expression of BLT1 in microglia (Arita *et al.*, 2007).

4.2 Actions of RvD1 and RvE1 at the periphery

The anti-inflammatory activities of RvD1 and E1 have been reported both *in vitro* and *in vivo* mostly on peripheral cells. Their pro-resolving effects are widely described in macrophages in rodent models of inflammation (for reviews: Claria *et al.*, 2011; Fredman and Serhan, 2011; Lee and Surh, 2012; Recchiuti, 2013; Seki *et al.*, 2009; Serhan, 2014).

In vitro studies report that RvD1 and RvE1 inhibit neutrophil transmigration and infiltration to the inflamed site (Arita *et al.*, 2005; Wang *et al.*, 2011). They also limit monocyte chemotaxis and adhesion (Dona *et al.*, 2008; Claria *et al.*, 2012). They potently decrease pro-inflammatory cytokine expression (Recchiuti *et al.*, 2011; Schwab *et al.*, 2007; Tian *et al.*, 2009; Titos *et al.*, 2011) and enhance macrophage phagocytic activity (Ohira *et al.*, 2010; Krishnamoorthy *et al.*, 2010). RvE1 and RvD1 also induce a functional switch in macrophage polarization from M1 to M2 (Navarro-Xavier *et al.*, 2010; Titos *et al.*, 2011) and can switch macrophages from $CD11b^{high}$ to $CD11b^{low}$ phenotype (Schif-Zuck *et al.*, 2011). In a model of BV-2 microglia cells, Li *et al.* demonstrate that RvD1 promotes IL-4-induced microglia alternative activation involved in tissue remodeling and healing (Li *et al.*, 2014). RvD1 and RvE1 can also inhibit the expression and the release of pro-inflammatory cytokines in microglia (Xu MX *et al.*, 2013; Xu ZZ *et al.*, 2013).

In vivo, RvD1 significantly reduces polymorphonuclear neutrophils (PMN) infiltration in murine air-pouch inflammation (Serhan *et al.*, 2002). RvD1 administration decreases pro-inflammatory cytokine production in acute models of injury in lung (Wang *et al.*, 2011, 2014; Yaxin *et al.*, 2014; Zhou *et al.*, 2013), kidney (Chen *et al.*, 2014) and in a model of allergic airways (Rogerio *et al.*, 2012). RvD1 enhances phagocytosis of apoptotic leukocytes and bacteria (Chiang *et al.*, 2012; Krishnamoorthy *et al.*, 2010).

RvE1 also exerts potent anti-inflammatory actions *via* the regulation of cytokine production in experimental models of colitis (Arita *et al.*, 2005) and peritonitis (Schwab *et al.*, 2007). RvE1 increases neutrophil apoptosis, enhances phagocytosis by macrophages (enhanced bacterial clearance) and decreases levels of pro-inflammatory cytokines (El Kebir *et al.*, 2012; Seki *et al.*, 2010).

4.3 Actions of resolvins in the central nervous system

Very few studies described the role of resolvins in the central nervous system, in particular in microglia cells. RvD1 and its receptor were detected in the cerebrospinal fluid of control and Alzheimer patients (Wang *et al.*, 2015b). The importance of the resolution pathway in maintaining normal cognition is suggested by the highlighted positive correlation between Mini-Mental State of Examination (MMSE) and the levels of RvD1 in the cerebrospinal fluid, suggesting that resolution can inhibit Alzheimer disease-related cognitive decline. Other studies published data reporting that a supplementation in n-3 PUFAs in patients with minor cognitive impairment increases RvD1 in macrophages (Fiala *et al.*, 2015) and in vitro RvD1 with vitamin D promotes Aβ-phagocytosis in isolated Alzheimer's patient macrophages (Mizwicki *et al.*, 2013). A study of Harrison *et al.* (2015) demonstrates that RvE1, administered intraperitoneally for consecutive days, decreases the traumatic brain injury-induced activation of microglia. RvE1 increases the proportion of ramified microglia and decreases the proportion of rod microglia in the sensory cortex. Moreover, RvE1 significantly alters the inflammatory profile of microglia (Harrison *et al.*, 2015).

4.4 Mechanisms of actions of RvD1 and RvE1

The mechanisms by which RvD1 acts are not yet clearly established. It was shown that RvD1 acts *via* its receptor ALX/fpr2 to regulate specific miRNAs that are key regulators for resolution of inflammation (Bartel, 2009; Recchiuti, 2013). miRNA are small ~23 nt endogenous RNA that can play important gene regulatory roles by pairing to the mRNA of protein coding genes to direct their posttranscriptional repression. miRNAs has recently emerged as a major class of gene expression regulators linked to most biological functions including immune regulation (Ceppi *et al.*, 2009; O'Neill *et al.*, 2011; Recchiuti *et al.*, 2011; Recchiuti and Serhan, 2012). miRNAs in macrophages downregulate the mRNA translation of key inflammatory cytokines (Fredman and Serhan, 2011).

miR-155, miR-21 and miR-146 have been central in much miRNA research due to their expression levels following LPS-induced inflammation (Quinn and O'Neill, 2011). Ceppi *et al.* (2009) reported that both miR-155 and miR-146 are up-regulated upon LPS stimulation in human primary dendritic cells (Ceppi *et al.*, 2009). miR-155 targets the proteins involved in the activation of NFκB, thus controlling tissue damage due to inflammation (Faraoni *et al.*, 2009). It is characterized as a common target of a broad range of inflammatory mediators (O'Connell *et al.*, 2007). miR-146 is

involved as a negative regulator fine tuning the immune response (Quinn and O'Neill, 2011). These miRNAs play a key role in modulating the IL-1 and IL-6 pathways. miR-21 is also involved as a central player in the inflammatory response (Quinn and O'Neill, 2011). miR-21 plays a key role in the resolution of inflammation and in negatively regulating the pro-inflammatory response in particular in macrophages (Sheedy and O'Neill, 2008). Resolvins have been shown to regulate specific miR-target genes involved in inflammation and resolution (Recchiuti *et al.*, 2011). These include miR-21, miR-146, miR-208 and miR-219, which represent a new class of pro-resolving miRNAs.

Results from Serhan and coworkers help to identify the possible pathways and lead to a hypothetical scheme for RvE1/ChemR23 dependent signaling in human macrophages (Fredman and Serhan, 2011; Oh *et al.*, 2011; Ohira *et al.*, 2010). RvE1 regulates phosphorylation of Akt and ribosomal protein rS6 *via* RvE1-specific interaction with ChemR23 on both human ChemR23-transfected CHO cells and human macrophages enhancing phagocytosis (Ohira *et al.*, 2010). A decrease in p42 and p44 MAP kinase phosphorylation, induced by a bacteria, is also observed when neutrophils in culture are pretreated 15 min before challenge bacteria with 100 ng/ml RvE1 (Herrera *et al.*, 2015).

5 Conclusion

More studies are needed to understand the actions of resolvins in the central nervous system. Indeed, resolvins are promising therapeutic compounds: these mediators are of natural origin and are active at very low concentrations (nM) as compared to their precursors (μM) (Ariel and Serhan, 2007; Bannenberg and Serhan, 2010). Resolvins administered orally to mice reduce acute inflammation and accelerate or initiate resolution (Recchiuti *et al.*, 2014). These results highlight the possibility to exploit the beneficial effect of RvD1 in Human. Resolvins open novel strategies for the treatment of inflammatory diseases.

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Cite this article as: Corinne Joffre, Charlotte Rey, Agnès Nadjar, Sophie Layé. Role of n-3 PUFAs in inflammation *via* resolvin biosynthesis. OCL 2016, 23(1) D104.