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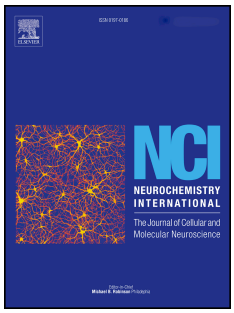

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PII: S0197-0186(15)30032-2

DOI: 10.1016/j.neuint.2015.08.004

Reference: NCI 3752

To appear in: *Neurochemistry International*

Received Date: 28 June 2015

Revised Date: 4 August 2015

Accepted Date: 5 August 2015

Please cite this article as: Vauzour, D., Martinsen, A., Layé, S., Neuroinflammatory processes in cognitive disorders: Is there a role for flavonoids and n-3 polyunsaturated fatty acids in counteracting their detrimental effects?, Neurochemistry International (2015), doi: 10.1016/j.neuint.2015.08.004.

Neuroinflammatory processes in cognitive disorders: Is there a role for flavonoids and n-3 polyunsaturated fatty acids in counteracting their detrimental effects?

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Keywords (max 6): Neuroinflammation; microglia; flavonoids; n-3 polyunsaturated fatty acids; cognitive disorders; Alzheimer's disease.

Abstract

Neuroinflammatory processes are known to contribute to the cascade of events culminating in the neuronal damage that underpins neurodegenerative disorders such as Parkinson's and Alzheimer's disease. With the ageing population and increased cases of neurodegenerative diseases, there is a crucial need for the development of new strategies capable to prevent, delay the onset or treat brain dysfunction and associated cognitive decline. Growing evidence sheds light on the use of dietary polyphenols and n-3 long chain polyunsaturated fatty acids to improve cognitive performances and reduce the neuroinflammatory and oxidative stress responses occurring with age and neurodegenerative pathologies. This review will summarise the most recent information related to the impact and mechanisms underlying the neuroinflammatory processes in neurodegenerative disorders. We will also detail the current evidence indicating that flavonoids and n-3 polyunsaturated fatty acids are strong candidate in preventing neuroinflammation and modulating age-related memory decline, and will describe the potential mechanisms of action underlying their neuroprotective effects. As such, these dietary bioactives represent important precursor molecules in the quest to develop of a new generation of drugs capable of counteracting neuroinflammation and neurodegenerative diseases.

1. Introduction

Neuroinflammation constitutes a beneficial process involved in the maintenance of organ homeostasis and the brain response to infection or injury (Glass et al., 2010). However, sustained neuroinflammatory processes may contribute to the cascade of events leading to the progressive neuronal damage observed in ageing (Barrientos et al., 2015) and aged-related cognitive disorders such as Parkinson's disease (PD) (Herrero et al., 2015) and Alzheimer's disease (AD) (Heneka et al., 2015; Heppner et al., 2015). Existing drug treatments for AD such as cholinesterase inhibitors and NMDA receptor antagonists (Legos et al., 2002; Narayan et al., 2002) and for PD such as dopaminergic drugs (Wu and Frucht, 2005) do not target the underlying degeneration of neurons, and consequently there is a great need to develop alternative strategies capable of preventing the progressive loss of specific neuronal populations. Since chronic inflammation is a major hallmark of AD and PD and long-term use of non-steroidal anti-inflammatory drugs have been shown to lower the risk of AD in later life, there has been much interest in the development of new drugs capable of preventing neuroinflammatory mediated brain injury. Various therapeutic approaches that directly or indirectly influence inflammatory responses have/are being developed and tested (see review (Glass et al., 2010)). Recently, much interest has focused on the suggested anti-inflammatory and neuroprotective effects of dietary-derived polyphenols and the long chain (LC) n-3 polyunsaturated fatty acids (PUFA), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), rendering these molecules as potential candidates for use in preventative and therapeutic strategies to reduce the risk of chronic neurodegenerative diseases. This review will summarise the most recent information related to the impact and mechanisms underlying the neuroinflammatory processes in neurodegenerative disorders. In addition, the following sections will also review the role of flavonoids and n-3 PUFA in preventing neuroinflammation and modulating age-related memory decline, and will describe the potential mechanisms of action underlying their neuroprotective effects.

2. Microglia activation in ageing, cognitive and neuropsychiatric disorders

Proinflammatory cytokines produced by activated innate immune cells in response to tissue injury, infection or inflammation act on the brain through several pathways (humoral, neural and cellular) (Dantzer et al., 2008). Activation of immune-to-brain communication ultimately induces the production of brain cytokines by activated glial cells, and particularly microglia (Dinel et al., 2014; Laye et al., 1994). In the event of non-sterile stimuli (pathogens such as virus and bacteria), microglial cells are activated producing pro and/or anti-inflammatory cytokines but also lipid derived products such as prostaglandins (PG). Although microglial response promotes the

clearance of pathogens, toxic cellular debris and apoptotic cells, a complete blockade of microglial activity exacerbates brain damage in adult and several ischemic injury models (Lalancette-Hebert et al., 2007). In addition, activated microglia has also been reported to trigger transient behavioural changes (weakness, listlessness, malaise, anorexia, fatigue and transient cognition and mood alterations) so called sickness behaviour (Dantzer et al., 1998).

The sustained production of inflammatory factors such as proinflammatory cytokines adversely affects neuronal functioning as observed in ageing, obesity, cognitive and neuropsychiatric disorders (Castanon et al., 2015; Dantzer et al., 2008). The production of proinflammatory cytokines in the brain is therefore a double-edged sword representing a fine balance between protective and detrimental effects and therefore needs to be tightly regulated. Microglial phenotypes could play a crucial role in the protective or detrimental role of microglial response toward neurons (Figure 1). Accordingly, whilst activated M1 cells produce proinflammatory cytokines (interleukin (IL)-1β, IL-6, IL-12 and tumor necrosis factor (TNF-α)) and have cytotoxic properties, M2a cells associated with the production of IL-10 and IL-4 are involved in repair and regeneration (Fenn et al., 2012; Perry et al., 2010). The failure of microglia to polarise from a proinflammatory to an anti-inflammatory phenotype supports the detrimental role of activated microglia in normal brain ageing and neurodegenerative disorders with a self-sustaining and self-amplifying cycle of neurotoxicity. For instance, when challenged with either immune stimuli or a stress, aged animals clearly mount an exaggerated neuroinflammatory response, also called inflammaging and characterised by the overproduction of proinflammatory factors (IL-1β, IL-6, TNF-α, inducible nitric oxide synthase (iNOS)), with a longer duration of activation compared to young congeners (Barrientos et al., 2009; Godbout et al., 2005; Sparkman et al., 2005). This phenomenon, first described in a mouse model of prion disease is called microglia priming or sensitization (Cunningham et al., 2005). In addition to producing proinflammatory cytokines, senescent microglia also express lipofuscin granules, higher levels of CD86, major histocompatibility complex II (MHC II), toll-like receptors (TLRs) and complement receptor 3 (CR3/CD11b) and display a decreased number and complexity of processes as described in activated microglia (Hanisch and Kettenmann, 2007; Tremblay et al., 2011). They also have reduced phagocytic activities of amyloid beta (Aβ) as demonstrated in aged transgenic mice (Heneka et al., 2010). The mechanisms involved in increased microglia activation in the ageing brain are not fully understood, although the impaired expression of CD200 and CX3CR1, known to be produced by neurons to maintain microglia in the non-activated state in the healthy brain, might be involved (Dilger and Johnson, 2008). Failure to tightly regulate systemic immune activation and/or brain microglia

activation leads to significant and prolonged induction of brain cytokines, which is accompanied by an extended sickness behaviour, leading to depression or chronic pain, and impaired motor and cognitive abilities, resulting in normal brain ageing and age-related neurodegenerative diseases (Capuron and Miller, 2011; Delpech et al., 2015b; Laye, 2010). This further stimulates research aiming at developing drugs targeting the M1 phenotype.

Growing evidence also points out the indirect activation of microglia by increased insulin resistance in healthy ageing brain and aged-related cognitive disorders. The increased brain insulin resistance induces glycogen synthase kinase 3 (GSK-3β), which causes Tau hyper-phosphorylation, increased β amyloid production and local plaque-associated microglial-mediated inflammatory responses (de la Monte, 2012). The increased insulin resistance might also stem from the loss of low-density lipoprotein receptor-related protein 1 (LRP1), the expression of which is suppressed in AD (Liu et al., 2015). In addition to insulin, the role of cyclin-dependent kinase 5 (Cdk5) and its activator p25 as upregulators of cytosolic phospholipase A2 (cPLA2), which catalytically hydrolyses the ester bond at the *sn*-2 position of membrane glycerophospholipids to release a free fatty acid such as arachidonic acid (AA) and a lysophospholipid, has also been reported in neurodegenerative diseases such as AD and PD (Sundaram et al., 2013). Generated AA is then metabolised by cycloxygenases (COX) and lipoxygenases (LOX) into PG, leukotrienes, thromboxanes (TX) and lipoxins that further trigger the oxidative stress and neuroinflammatory response (Ong et al., 2015). Furthermore, increased activation of Cdk5 is responsible for Tau hyper-phosphorylation and subsequent Tau misfolding and fibril aggregation, the hallmarks of AD (de la Monte, 2012). As a consequence, either GSK-3β or p25 and the aberrant activation of Cdk5 as well as cPLA2 represent interesting therapeutic targets against microglia-induced neuroinflammation.

3. Neuroinflammatory response

The underlying mechanisms of neuronal degeneration associated with motor and cognitive decline remain elusive, although it is thought that several cellular and molecular events are involved which are sensitive to oxidative stress and chronic neuroinflammation. Figure 2 summarises the main mechanisms underlying the neuroinflammatory response responsible for depressive-like behaviours and motor and cognitive disorders.

Chronic activation of microglia leads to de novo production of proinflammatory cytokines (i.e. IL-1β, IL-6 and TNF-α), chemokines, nitric oxide (NO), eicosanoids (i.e. PGE2) and reactive oxygen species (ROS) (Barrientos et al.,

2015; Vauzour, 2012). For example, increased level of IL-1β elevates the production of ROS, which in turn, activates mitogen-activated protein (MAP) kinases such as c-Jun N-terminal kinase (JNK) and p38, resulting in cell damage and cell death therefore impairing the long-term potentiation (LTP) and leading to cognitive decline. In addition, the excessive production of proinflammatory cytokines such as TNF-α and IL-1β has been reported to result in glutamate cytotoxicity by directly stimulating NMDA receptors while inhibiting GABA-A receptors (Barrientos et al., 2015; Olmos and Llado, 2014).

Another mechanism by which cytokines may impair synaptic plasticity (Delpech et al., 2015b) is their capacity to induce the synthesis of indoleamine 2,3-dioxygenase (IDO), a rate-limiting enzyme degrading tryptophan along the kynurenine pathway, in activated microglia. Although cytokine-induced activation of IDO is usually beneficial to the host (Harrington et al., 2008), sustained brain IDO activation can also be deleterious by negatively impacting the monoaminergic neurotransmission (e.g. serotonin, dopamine) and neuronal survival (Capuron and Miller, 2011; Dantzer et al., 2008). Indeed, increased brain or cerebrospinal fluid concentrations of kynurenine and its neurotoxic metabolites have been reported in several neurodegenerative and psychiatric disorders (Campbell et al., 2014; Capuron et al., 2011) suggesting that IDO activation may lead to both functional and structural alterations in the brain. Activation of the kynurenine pathway has indeed been recently reported to affect human neurogenesis in the hippocampal formation (Zunszain et al., 2012), an important brain structure involved in cognitive functions and an important site for IDO production (Andre et al., 2008; Frenois et al., 2007). In addition, pharmacological or genetic inhibition of IDO activity prevents induction of depressive-like behaviours and cognitive impairments (reviewed in (Castanon et al., 2014; Dantzer et al., 2008).

Recently, the role of guanosine triphosphate cyclohydrolase I (GTP-CH1) in the cognitive effect of chronic inflammation has also been revealed in elderly (Capuron and Miller, 2011). GTP-CH1 is the rate-limiting enzyme of GTP conversion into 7,8-dihydroneopterin (BH2), which leads to the production of neopterin at the expense of tetrahydrobiopterin (BH4) (Oxenkrug, 2011). BH4 is a cofactor of aromatic amino acid hydroxylase and therefore plays a fundamental role in dopamine synthesis (Neurauter et al., 2008). Cytokines-induced GTP-CH1 activation, classically assessed by measuring increased production of neopterin, is therefore able to impair the dopaminergic neurotransmission which is known to be involved in mood disorders and cognitive dysfunctions, including in conditions of chronic immune stimulation (Capuron and Miller, 2011).

Additionally, inflammation both at the periphery and in the brain is tightly regulated to be quickly resolved. The control and resolution of inflammation is due to the activation of several negative feedback mechanisms: secretion of anti-inflammatory cytokines, inhibition of proinflammatory signalling cascades, shedding of receptors acting as decoy targets for inflammatory mediators, glucocorticoids and activation of regulatory cells.

4. Effects of diet on neuroinflammation and neurodegenerative disorders

A large body of evidence has linked the consumption of food and beverage enriched in fats, sugars and salt to mood, motor and cognitive impairments in addition to metabolic disorders (Nguyen et al., 2014). However, a substantial amount of recent evidence also suggests that many food components and in particular flavonoids and n-3 PUFA, could be good candidates to modulate inflammation and to prevent and/or delay the onset of ageing and age-related neurodegenerative disorders.

4.1. Flavonoids as regulators of neuroinflammatory processes

Flavonoids comprise the most common group of polyphenolic compounds in the human diet and share a common feature which consist of two aromatic carbon rings, benzopyran (A and C rings) and a benzene ring (B ring), and may be divided in various subgroups based on the degree of the oxidation of the C-ring, the hydroxylation pattern of the ring structure and the substitution of the 3-position. The main dietary groups of flavonoids are as follows: 1) flavones (e.g. apigenin, luteolin), which are found in parsley and celery; 2) flavonols (e.g. kaempferol, quercetin), which are found in onions, leeks, broccoli; 3) isoflavones (e.g. daidzein, genistein), which are mainly found in soy and soy products; 4) flavanones/flavanonols (e.g. hesperetin, naringenin/astilbin, engeletin), which are mainly found in citrus fruit, herbs (oregano) and wine; 5) flavanols (e.g. (+)-catechin, (-)-epicatechin, epigallocatechin, epigallocatechin gallate (EGCG)), which are abundant in green tea, red wine, chocolate; and 6) anthocyanidins (e.g. pelargonidin, cyanidin, malvidin), whose sources include red wine and berry fruits. Further information regarding the structure and classes of flavonoids may be found in the thorough review by (Rodriguez-Mateos et al., 2014).

Although dietary flavonoids appear to be good candidates for neuroprotection in terms of their ability to modulate neuroinflammation in the central nervous system (CNS), their bioavailability and biological effects will greatly depend on their biotransformation by the liver and by the gut microbiota and their bioaccessibility to the brain

(Rodriguez-Mateos et al., 2014). Indeed, flavonoids and, to a lesser extent, their metabolites have been previously reported to cross the blood brain barrier (BBB) in agreement with their lipophilicity degree but independently of the administration route (Vauzour, 2012). Polar flavonoids and metabolites (*O*-methylated derivatives) such as hesperitin and naringenin, exhibit greater brain uptake than the less polar, sulphated and glucuronidated metabolites such as anthocyanins and glucuronide conjugates of hesperitin and naringenin (Youdim et al., 2004). However, the lipophilicity degree solely does not linearly correlate with the flavonoids content within the brain and the role of efflux transporters such as the P-glycoprotein needs to be taken into account (Youdim et al., 2004).

4.1.1. Does flavonoid intake prevent neuroinflammation? Epidemiological and clinical evidence

Recent prospective cohort data suggest that the improved cognitive function and reduced risk from age-related neurodegenerative diseases, associated with increased fruits and vegetables intake (Sofi et al., 2010; Tangney et al., 2011) may be in large part attributable to intake of specific flavonoids (Barberger-Gateau et al., 2007). In particular, increased consumption of total flavonoids was positively associated with episodic memory in middle-aged adults (Kesse-Guyot et al., 2012) and with a reduced rate of cognitive decline in adults aged 70 and over (Devore et al., 2012). In addition, data from a cross sectional study indicated that total flavonoid intake was inversely associated with plasma C reactive protein (CRP) concentrations (Chun et al., 2008). In support of this result, a number of dietary intervention studies have provided further evidence that dietary flavonoids are capable of modulating cytokine production, although the results remain inconsistent. For example, a higher consumption of fruits, vegetables and legumes is inversely associated with blood inflammation markers such as CRP, IL-6 and adhesion factors (Macready et al., 2014; Nanri et al., 2008; Salas-Salvado et al., 2008). In addition, intervention trial with an anthocyanin extract from blueberries (300mg/d for 3 weeks) significantly reduced the plasma concentration of nuclear factor (NF)-kB-related proinflammatory cytokines and chemokines (IL-4, IL-13, IL-8 and IFN-α) in a group of 120 men and women aged 40-74 years (Karlsen et al., 2007). However, short-term consumption of black tea (900 mL/d, 4 weeks) did not improve plasma CRP levels in a group of sixty-six patients with coronary artery disease (Widlansky et al., 2005). No significant effect has been observed in plasma levels of CRP or intercellular adhesion molecule 1 (ICAM-1) among healthy volunteers consuming diets rich or poor in berries and apple for 6 weeks (Freese et al., 2004). Similarly, 4-week administration of quercetin significantly increased plasma levels of quercetin, but did not alter *ex vivo* LPS-induced TNF-α levels (Boots et al., 2008).

However, in AD patients, the daily consumption of combined extracts of green tea and apple for 8 months was reported to reduce the serum levels of proinflammatory cytokines (IL-2, IFN-γ and TNF-α), while not affecting the anti-inflammatory cytokines IL-4 and IL-10 in early stages of AD pathology (Rubio-Perez and Morillas-Ruiz, 2013). As far as therapeutic treatments on PD patients are concerned, a randomized controlled trial has recently been completed testing the neuroprotective effect of green tea EGCG in PD patients without taking any PD drug (ClinicalTrials.gov Identifier: NCT00461942). The inconsistent outcome of various trials on the preventive anti-inflammatory effect of flavonoid supplementation reinforces the necessity for more prospective randomised trials with larger sample sizes and longer follow-up in both healthy volunteers and in clinical conditions.

4.1.2. Mechanisms of action of flavonoids in controlling neuroinflammation

Since the neuropathology of many neurodegenerative disorders has been linked to increases in brain oxidative stress (Halliwell, 2006), historically, efforts have been directed at exploring antioxidant strategies to combat neuronal damage. However, the concentrations at which flavonoids exert such antioxidant activity is unlikely to be easily achieved *in vivo* as many flavonoids have very limited bioavailability and are extensively metabolised therefore reducing their antioxidant potential (Williams et al., 2004). During the last years, a new realisation of how nutritional antioxidants may function has been envisaged, and recent findings have suggested that in lower amounts, typical of those attained in the diet, flavonoids may exert pharmacological activity within the cells (Vauzour, 2012). To date, evidence related to the anti-neuroinflammatory effect of flavonoids predominantly derives from *in vitro* and animal studies and currently supports: 1) a capacity to downregulate the activity of proinflammatory transcription factors such as NF-κB, nuclear factor erythroid 2-related factor 2 (Nrf2) or STAT through their influences on a number of glial and neuronal signalling pathways, 2) an inhibitory role on the release of cytokines, such as IL-1β and TNF-α, from activated microglia, 3) an inhibitory action against the production of NO and PGE2 in response to microglia activation, 4) an ability to inhibit the activation of NADPH oxidase and subsequent ROS generation in activated glial cells, and 5) an inhibitory action against activated microglia through TLR receptors or insulin resistance (Gonzalez-Gallego et al., 2010; Vauzour, 2014).

Most recent findings on the impact of flavonoids on the suppression of NF-κB gene and protein expression have been performed in LPS-stimulated cells and/or experimental animal models. For example, LPS-induced increases of NF-κB gene and protein expression was reduced in presence of baicalein (10-50 μM) and wogonin (10-30 μM),

two flavones extracted from *Scrutellaria baicalensis* in BV-2 microglial cells (Suk et al., 2003; Yeh et al., 2014). In addition, orientin (10-40 µM; extracted from *Trollius chinensis*), tangeretin (80 µM; a flavonoid from citrus fruit peels) and quercetin (20-30 µM) all reduced LPS-induced NF-κB expression in BV-2 microglial cells (Kang et al., 2013; Shu et al., 2014; Zhou et al., 2014). Of particular interest, it has recently been demonstrated that EGCG (10 µM) attenuates LPS-induced inflammatory and oxidative stress responses by modulating Nrf2 and decreasing S-nitrosylation levels of proteins involved in free radical scavenging such as superoxide dismutase (SOD) in BV-2 microglial cells (Qu et al., 2014). In experimental rat models, naringenin (50 mg/kg ip for 21 days) (Raza et al., 2013) or kaempferol glycosides from *Carthamus tinctorius* L. (7.5 or 10 mg/kg i.v. acute) showed a beneficial impact on neuroinflammation by inhibiting STAT3 and NF-κB after ischemic brain injury in rat (Yu et al., 2013). Similarly, a 6-month diet enriched in the flavonoid fisetin (0.05%, ≈ 25 mg/kg) reduced the protein expression of inflammatory markers in huAPPswe/PS1ΔE9 transgenic mice in an extracellular signal related kinase (ERK)-p25-mediated pathway without affecting the mRNA expression of NF-κB1 (Currais et al., 2014).

In agreement with the downregulation of inflammatory transcription factors, the release of pro-inflammatory cytokines is also depressed in the presence of flavonoids. For example, treatment with apigenin (25 µM) or luteolin (25 µM) alleviated microglia-induced neuroinflammatory response (TNF-α, IL-6) by suppressing CD40 receptor expression in a STAT1-dependent manner (Rezai-Zadeh et al., 2008). Similarly, wogonin (3-10 µM) was shown to alleviate the inflammatory response in activated microglial cells by reducing ERK phosphorylation, while not affecting JNK/p38 activies, although at a higher concentration (30 µM) the expression of the three MAPKs were decreased (Yeh et al., 2014). In high fat fed C57Bl/6 mice supplemented with luteolin (10mg/kg) for 16 weeks, spatial memory was improved along with a decreased expression of inflammatory markers TNF-α, IL-1β, IL-6 and NF-kB, oxidative stress and neuronal insulin resistance, and an increased production of BDNF and synaptic proteins (Liu et al., 2014). Accordingly, kaempferol-3-*O*-rutinoside (10 mg/kg) and kaempferol-3-*O*-glucoside (7.5 mg/kg) significantly inhibited the level of IL-1β, iNOS, ICAM-1 and the metallopeptidase 9 (MMP-9) in ischemic brain-injured rats (Yu et al., 2013). Furthermore, oral administration of scuttelarin (5 or 20 mg/kg), a flavone extracted from *Erigeron breviscapus*, decreased the hypertension-induced expression of NF-κB, TNF-α, IL-1β and IL-18 in the cortex and the striatum of rat. Such effect was observed to be mediated through TLR4 and by blocking neuronal apoptotic proteins such as cleaved caspase-3, p17, Bax and myeloid cell leukemia-1 (Mcl1) (Chen et al., 2013). In addition to the inhibition of proinflammatory cytokines, the green tea derived EGCG (100 µM) was reported to inhibit the expression of inflammatory chemokines such as CXCL10, CCL22, CCL17 and

transforming growth factor β (TGF-β) in HaCaT keratinocytes (Noh and Park, 2012). Li and collaborators also demonstrated that EGCG (5-25 μM) downregulates the expression of monocyte chemotactic protein (MCP-1/CCL2), ICAM-1 and vascular cell adhesion molecule 1 (VCAM-1) in human cerebral microvascular endothelial cells, protecting BBB integrity during pathological inflammation (Li et al., 2012). However, this effect was not dependent on TLR4 expression as reported previously (Chen et al., 2013). EGCG (2-6 mg/kg) was also recently reported to alleviate cognitive impairments in huAPPswe/PS1ΔE9 transgenic mice by reducing the expression level of insulin receptor substrate 1 (IRS-1) and increasing the phosphorylation of Akt and GSK-3β in the hippocampus (Jia et al., 2013).

As previously observed with 10 μM and along with reducing LPS-generated free radicals (Ha et al., 2008; Kao et al., 2010), quercetin (20-30 μM) also attenuated the LPS-induced NO production and iNOS protein and gene expressions in a Nrf2-dependent signalling pathway in BV-2 microglial cells (Kang et al., 2013). In addition to the inhibition of iNOS and subsequent NO production, apigenin (10 μM) (Ha et al., 2008) and wogonin (10-30 μM) (Yeh et al., 2014), also decrease the COX-2-dependent PGE2 production in LPS-activated BV-2 cells. One possible explanation for the impact of flavonoids on NO and PGE2 production could stem from the inhibition of upstream signalling molecules such as MAPKs, as observed by the decrease of JNK and p38 phosphorylation in presence of apigenin (10 μM) on LPS-induced microglial cells (Ha et al., 2008). As a downstream targeted signalling pathway, quercetin (10 μM) was shown to decrease the expression of lipid raft markers such as ganglioside GM1 and caveolin-1 suggesting that this flavonoid, by intercalating within the plasma membrane, might disrupt lipid raft integrity and ligand-receptors interactions involved in the neuroinflammatory response (Kao et al., 2010) (Figure 2).

In addition to isolated compounds, studies investigating the impact of blueberry and apple flavonoids reported an attenuation of neuroinflammation and improved cognitive functions, possibly by lowering the expression of IL-1β and TNF-α in rat hippocampus (Jung et al., 2009; Shukitt-Hale et al., 2008). A blueberry extract significantly depressed the LPS-induced p44/p42 MAPK and subsequent TNF-α and IL-6 levels in murine primary culture of microglial cells (Zhu et al., 2008). More recently, a flavonoid-enriched fraction from apple peel (25 mg/kg/d for 31 days) provides strong anti-neuroinflammatory effects in a mouse model of autoimmune encephalomyelitis by decreasing mRNA expression of proinflammatory cytokines (IL-1β, TNF-α and IL-6) and protein expression of

chemokines (CXCL1, CXCL2, CXCL9, CCL2 and CCL3) in the cerebellum and/or spinal cord of mice (Warford et al., 2014).

The majority of the existing evidence for the anti-inflammatory effects of flavonoids (Figure 2) stems from *in vitro* studies in primary glial cells or microglial cell lines in which unrealistic, nonphysiologically achievable concentrations of flavonoids were used. To elucidate the molecular mechanisms of flavonoids action in the brain, future cell studies should use both flavonoid forms and concentrations relevant to those found in circulation after consumption of a flavonoid-rich food. In particular, tested flavonoids should include flavonoid conjugates and metabolites arising as a result of hepatic and colonic metabolism. Although *in vitro* studies provide an insight on the cellular mechanisms of action of flavonoids in the CNS, they do not prove the actual potential of these promising compounds to inhibit neuroinflammation *in vivo*. Further work is therefore warranted to support their efficacy in humans.

4.2. n-3 PUFA are potent regulators of neuroinflammatory processes

LC n-3 PUFA modulate the inflammatory processes by acting at the immune system level through the regulation of inflammatory gene expression, especially cytokines and chemokines, the decrease of inflammatory PG and eicosanoids and the induction of pro-resolutive factors, resolvins and protectins that are involved in the resolution of inflammation (Calder, 2013; Serhan, 2007; Serhan et al., 2007). LC n-3 PUFA anti-inflammatory effects are thought to require their incorporation into plasma membranes of target tissues, however they have short-term effect as they are rapidly metabolized into bioactive products. In particular EPA, DHA and their bioactive mediators have potent anti-inflammatory and pro-resolving properties in the periphery (Serhan and Chiang, 2013) and in the brain (Bazinet and Laye, 2014; Laye, 2010; Orr and Bazinet, 2008; Rapoport, 2008). Loss of these regulatory processes can result in excessive, inappropriate or on-going inflammation that can cause irreparable damage to host tissues, including the brain.

EPA is a substrate for the COX, LOX and cytochrome P450 enzymes that produce 3-series eicosanoids (PG and TX) and 5-series leucotrienes that are increased in macrophages or neutrophils enriched in EPA and DHA by dietary means (Calder and Grimble, 2002; Yates et al., 2014). In addition, other anti-inflammatory and pro-resolving derivates so-called resolvins, protectins and maresins are produced from EPA and DHA from the COX

and LOX pathways. Resolvin E1 (RvE1), RvE2 and RvE3 are produced from EPA and RvD1, RvD2 and RvD5 are biosynthesized from DHA (reviewed in (Serhan, 2007; Serhan et al., 2011). When produced in the brain, protectins are referred to as neuroprotectins (Bazan, 2012).

The cellular concentrations of LC n-3 and n-6 PUFA and their metabolites are determined by their relative dietary intake. Increased dietary intake of LC n-3 PUFA has been shown to significantly alter DHA levels in the brain(Freund Levi et al., 2014) suggesting that DHA and EPA dietary supplementation could be used to directly influence neuroinflammatory pathways (Bazinet and Laye, 2014). DHA entry in the brain is still a matter of debate. Non esterified DHA freely enters the brain (Bazinet and Laye, 2014; Song et al., 2010) and recently, an orphan receptor, the major facilitator superfamily domain-containing protein 2a (Mfsd2a) has been described as important to transport DHA through the BBB (Nguyen et al., 2014). In retinal cells, adiponectin receptor 1 is key for DHA uptake and retention (Rice et al., 2015). Once in the brain, DHA exerts anti-inflammatory/pro-resolutive activities through several action modes briefly described below. We will focus on the effect of LC n-3 PUFA on neuroinflammatory processes, especially DHA as this LC n-3 PUFA accumulates in the brain, while EPA does not.

4.2.1. Does LC n-3 PUFA supplementation prevent neuroinflammation? Epidemiological and clinical evidence

Several reports in humans highlight that higher dietary intake or blood/brain level of EPA and/or DHA are correlated with lower risk of developing neurodegenerative diseases with an inflammatory component including AD and PD recently reviewed in (Bazinet and Laye, 2014; Laye, 2010; Orr and Bazinet, 2008). Epidemiological studies have provided more consistent support for the effect of LC n-3 PUFA supplementation on neuroinflammation or microglia activity than randomised controlled trials (Sijben and Calder, 2007). Several epidemiological and observational studies reported that a higher level of blood LC n-3 PUFA is associated with lower proinflammatory cytokine production (Alfano et al., 2012; Farzaneh-Far et al., 2009; Ferrucci et al., 2006; Kiecolt-Glaser et al., 2011; Kiecolt-Glaser et al., 2007). In a cohort of elderly subjects, depressive individuals characterised by an elevated plasma n-6:n-3 ratio were found to exhibit higher levels of TNF-α and IL-6 (Kiecolt-Glaser et al., 2007). Additionally, LC n-3 PUFA supplementation in elderly subjects reduced the levels of inflammatory cytokines produced by blood leukocytes stimulated *in vitro* (Meydani et al., 1991). Furthermore, F2-

isoprostane, a PG-like compound referred to as an oxidative marker, and leukocyte telomere length, an indicator of immune cell ageing, were decreased in the blood of subjects supplemented with EPA/DHA (1.25 or 2.5g/d with a 7:1 EPA:DHA ratio for 4 months) (Kiecolt-Glaser et al., 2013). Similarly, the production of PGE2 by monocytes is inversely correlated to the EPA content of leukocytes obtained from aged subjects after the consumption of dietary complements containing different doses of EPA (Rees et al., 2006). AD patients supplemented with a DHA-rich diet display reduced release of proinflammatory cytokines (IL-1β, IL-6, GM-CSF) from stimulated peripheral blood mononuclear cells (Vedin et al., 2008). However, although most randomised trials with LC n-3 PUFA reported consistent decrease in inflammation in groups with high baseline inflammation (stressed students, elderly, diabetics, and hypertriglyceridemic subjects), results are mixed (Fritsche, 2006). Indeed, DHA/EPA dietary supplementation (1.1 g/d EPA and 0.7 g/d DHA) in healthy subjects blunted the endocrine stress response and body temperature increase in response to bacterial endotoxin (LPS) injection, without affecting cytokine production (Ferguson et al., 2014; Michaeli et al., 2007). Conversely, students who received EPA:DHA (7:1) capsules compared to placebo capsules showed lower anxiety during high stress period and decreased IL-6 but not TNF-α production in *ex vivo* LPS-stimulated immune cells, whereas serum levels were not affected (Kiecolt-Glaser et al., 2011). However, when taking the n-6:n-3 ratio into account, they observed decreased plasma cytokine levels of IL-6 and TNF-α after LC n-3 PUFA supplementation along with reduced anxiety (Kiecolt-Glaser et al., 2011), reinforcing the importance in randomised controlled trials of measuring basal level of LC n-6:n-3 PUFA before and after dietary interventions.

A potential explanation of conflicting results from randomised controlled trials might be that some condition-specific clinical end points are more sensitive markers to LC n-3 PUFA treatment than immune markers. For instance, a LC n-3 PUFA-enriched diet (Souvenaid® formulation) revealed improved cognitive decline in mild AD patients without taking any AD drug, by influencing synaptic plasticity as measured in an electroencephalography (EEG)-based functional network analysis along with cognitive tasks (Scheltens et al., 2012). Additionally, as lifestyle habits impact on cognition and the onset of dementia, the efficacy of a LC n-3 PUFA enriched diet on neuroinflammatory markers might be revealed if included in a multidomain intervention trial. The first large-scale and long-term randomised controlled trial to date that assessed and showed a beneficial impact of a multidomain intervention consisting of nutritional guidance, regular exercise, cognitive training and social activity along with monitoring metabolic and vascular risk factors, on cognitive performances and risk of cognitive decline in at-risk older individuals is the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability

(FINGER) study (Ngandu et al., 2015). Three other randomised controlled trials are currently measuring the effectiveness of a mulitdomain intervention including cognitive training, physical exercise, nutritional advice along with an omega-3 enriched diet with or without vitamin supplements, on cognitive and functional decline in elderly: the MAPT trial (ClinicalTrials.gov Identifier: NCT00672685), the DO-HEALTH trial (ClinicalTrials.gov Identifier: NCT01745263) and more recently the LILAC trial (Australia New Zealand Clinical Trial Registry-ACTRN12614001133628) (Hardman et al., 2015). The development of such strategies points out the importance of assessing the subject's lifestyle habits in particular from mid-life (Fratiglioni et al., 2004; Fratiglioni et al., 2007).

4.2.2. Mechanisms of action of n-3 PUFA in controlling neuroinflammation

Whether decreased brain DHA level through dietary means is proinflammatory in absence of proinflammatory stimuli has been poorly studied in animal models. *In vivo*, chronic dietary LC n-3 PUFA deficiency significantly affected microglia activity and increased the release of IL-6 and TNF-α in the blood of rat (McNamara et al., 2010) and in the hippocampus of mice at post-natal day 21 (Madore et al., 2014), which was not observed in the brain of adult and aged mice (Delpech et al., 2015c; Mingam et al., 2008; Moranis et al., 2012). Alternatively, both *in vivo* and *in vitro* studies have reported anti-inflammatory activities of LC n-3 PUFA in the brain especially in microglia (Laye, 2010; Orr and Bazinet, 2008) and currently supports: 1) a capacity to down-regulate the activity of proinflammatory transcription factors such as NF-κB, 2) an inhibitory role on the release of cytokines, such as interleukin IL-1β and TNF-α, from activated microglia, 3) an inhibitory action against the production of NO and PGE2 in response to microglia activation, 4) a beneficial action on membrane lipid composition, lipid rafts and membrane receptors incorporation such as TLR receptors, and 5) a capacity to elicit peripheral and central pro-resolutive processes by activating phagocytosis and promoting polarization of glial cells toward a M2-like phenotype. For example, in LPS-stimulated BV-2 microglial cells, DHA was reported to inhibit the NF-kB signalling pathway and associated increase in IL-1β and TNF-α (De Smedt-Peyrusse et al., 2008) and also to reduce the expression of inflammatory chemokines (CCL2, CCL3 or CXCL10) (Lu et al., 2013). In primary rat microglial cells, RvD1 inhibited the activity of NF-kB along with the expression of NO, IL-1β and TNF-α in response to LPS by blocking the activities of p38 and JNK MAPK and nuclear translocation of NF-kB (Xu et al., 2013). In rodents, high level of DHA by genetic or dietary means also depressed the expression of brain proinflammatory cytokines following systemic LPS administration (Delpech et al., 2015a; Mingam et al., 2008), brain ischemia-reperfusion (Lalancette-Hebert et al., 2011) or spinal cord injury (Huang et al., 2007; Lu et al.,

2013). The effect of DHA against neuroinflammation in response to spinal cord injury was mediated through p38 MAPK pathway, which improved locomotor deficits (Lu et al., 2013). In AD transgenic mice, DHA inhibited JNK and the phosphorylation of IRS-1 along with short-term memory improvement (Ma et al., 2009). Similarly, short-term exposure to dietary EPA reduced IL-1β-induced spatial memory deficit and anxiolytic behaviour (Song et al., 2004; Song et al., 2008) and improved LPS and Aβ-induced inhibition of LTP in both adult and aged rats (Minogue et al., 2007). Another important mediator of anti-inflammatory activity of DHA is neuroprotectin D1 (NPD1) (Bazan, 2006; Bazan et al., 2012). Infusion of DHA and NPD1 in the brain was reported to be acutely protective toward brain cytokine production and microglia activation (Lukiw et al., 2005; Orr et al., 2013) protecting brain from bacterial endotoxin-induced synaptic plasticity impairment and ageing (Delpech et al., 2015a; Delpech et al., 2015c; Labrousse et al., 2012). NPD1 was also shown to inhibit leukocyte infiltration, COX-2 expression, and NFκB activation *in vivo* and *in vitro* (Marcheselli et al., 2010).

DHA is highly incorporated in brain membranes and proper neuronal membrane lipid composition is crucial to maintain neuronal signalling (Bazan et al., 2011; Bazinet and Laye, 2014). As most receptors are embedded, damage to membranes would disrupt all forms of neuronal communication. For instance, with ageing, lipid composition and fat deposition distribution are disturbed in the brain, most likely due to decreased liver peroxisomal β-oxidation (Yang et al., 2014; Zamzow et al., 2014), which is responsible for specific fatty acids synthesis such as DHA (Ferdinandusse et al., 2001). In addition, along with the decreased level and activity of the enzyme delta 6-desaturase (Yehuda et al., 2005), the higher cholesterol content in the ageing neuronal membrane decreases membrane fluidity of the BBB (Yehuda et al., 2002). DHA not only modulates neuronal membranes but also influences membrane phospholipid composition of microglial cells and was reported to impair membrane location of TLR4, decreasing microglia activation by its ligand LPS in BV-2 microglial cells (De Smedt-Peyrusse et al., 2008). DHA also disrupts phospholipid rafts assembly in the plasma membrane in EL4 cells and primary B cells isolated from mice fed a high LC n-3 PUFA diet (Rockett et al., 2011; Ruth et al., 2009). The other family of receptors involved in tissue injury and subsequent inflammatory response is the Nod-like receptors. These receptors sense nucleotide-binding oligomerization domain proteins (NOD) bacterial products, the signalling pathway of which was reported to be modulated by DHA (Liu et al., 2012). DHA also affects the gene expression of receptors either located at the membrane such as GPR120 or GPR40 and/or the regulation of the peroxisome proliferator activated receptor (PPARγ) (Calder, 2013).

The anti-inflammatory activity of DHA and metabolites such as resolvins could also derive from their direct effect on invading macrophages or microglia, as investigated in the brain and spinal cord of inflammatory rodent models (Figueroa et al., 2012; Lim et al., 2013). Importantly, resolvin synthesis is increased in blood or peripheral tissues of both human and laboratory rodent with enriched levels of EPA and DHA by dietary means (Calder, 2015). The anti-inflammatory activity of these compounds is linked to the inhibition of proinflammatory cytokines (IL-1β and TNF-α) synthesis and the inhibition of trans-endothelial migration of neutrophils into tissues, preventing the infiltration of these cells in inflamed tissues therefore protecting from excessive inflammation (Ariel and Serhan, 2007; Calder, 2015). Some of the biological activities of resolvins are mediated by specific G-protein coupled receptors. Indeed, RvD1 activates lipoxin A4 receptor/formyl peptide receptor 2 (ALX/FPR2) and orphan receptor G protein-coupled receptor 32 (GPR32) to limit leukocyte infiltration in tissues and attenuate the production of proinflammatory cytokines (Fredman et al., 2014; Wang et al., 2014).

In the brain, LC n-3 PUFA could also yield protective influence indirectly, through the synthesis of bioactive derivates with pro-resolutive activities. For instance, RvD1 elicits macrophage polarization toward a M2-like phenotype by potentiating IL-4-induced expression of M2 markers in microglial cells and the signalling pathways involved in these processes, in particular the PPARγ signalling pathways (Li et al., 2014; Odusanwo et al., 2012; Wang et al., 2014) but also by promoting the synthesis of pro-resolving miRNAs, for example miR-181b involved in the regulation of ALX/FPR2 receptor (Pierdomenico et al., 2015). Recent data highlight that *in vitro* DHA also promotes microglia to a M2 phenotype with increased Aβ42 phagocytosis (Hjorth et al., 2013). Recently discovered as a new potent neuroprotective derivative of DHA, aspirine-triggered NPD1 (AT-NPD1) could also exert strong anti-inflammatory and pro-resolutive activities (Bazan et al., 2012) (Figure 2).

In the ageing brain, microglial activation, production of proinflammatory cytokines such as IL-1β and alterations in hippocampal LTP with age are attenuated by EPA (Lynch et al., 2007; Lynch et al., 2003). A 2-month fish-oil dietary supply increases DHA in the brain, prevented proinflammatory cytokines expression and astrocytes morphology changes in the hippocampus and restored spatial memory deficits and Fos-associated activation in the hippocampus of aged mice (Labrousse et al., 2012). To the extent that the level of peripheral cytokines reflects that of cytokines in the brain, these results suggest that dietary n-3 PUFA modulate neuroinflammation and associated behavioural effects in elderly individuals. However, the direct effect of DHA on the brain immune system is difficult to ascertain since primary injury in these animal models of neuroinflammation was also

improved. Chronic neuroinflammation in the brain of patients with AD could indicate that the resolution of inflammation is dysfunctional. To support this notion, while proinflammatory stimuli such as LPS promoted resolvin pathways activation in microglia, Aβ42 had an opposite or insignificant effect suggesting that pro-resolutive pathways are impaired in AD (Zhu et al., 2015). This is further substantiated by the observation that the lipoxin A4 (LXA4) level is decreased in postmortem brain tissue and cerebrospinal fluid samples from AD patients (Wang et al., 2015b). Very recently, it was shown that upon Aβ40 exposure, peripheral blood mononuclear cells from AD patients secreted less LXA4 and RvD1 together with the disease progression. Importantly, dietary supplementation of DHA prevented this reduction (Wang et al., 2015a), suggesting that LC n-3 PUFA protect from the AD-associated inflammation through the promotion of pro-resolving signalling pathways. Interestingly, LOX and LTB4 expression increases while LXA4 decreases in the brain of aged and AD mice models (Dunn et al., 2015).

Moreover, recent data show that 12 and 5-LOX are widely expressed in the brain where it mainly localizes in neuronal cells. *In vivo* over-expression of 5-LOX increases phosphorylation of specific Tau epitopes, and neuronal cells transfected with 5-LOX show a significant increase in Tau phosphorylation even when their ability to generate Aβ is completely blocked, suggesting that the effect on Tau is independent from Aβ (Chu et al., 2012). Interestingly, Tau-mice treated with zileuton (a potent 5-LOX inhibitor) displayed a significant improvement in memory and synaptic function together with a decreased tau phosphorylation level (Chu and Pratico, 2013; Giannopoulos et al., 2014). The use of PD146176, a specific 12/15 LOX inhibitor, also improved memory deficits and decreased Aβ plaques and neurofibrillary tangles in a genetic mice model of AD (Chu et al., 2015). All together, these data suggest the importance of using DHA and/or its mediator to target neuroinflammatory processes in the management of neurodegenerative diseases. This new therapeutic strategy is of particular importance since the target of proinflammatory pathways with COX-2 inhibitors is puzzling as 1) they poorly cross the BBB, 2) some of AA derivatives dependent on COX-2 are pro-resolutive and 3) COX-2 inhibitors are poorly efficient in AD (Aid and Bosetti, 2007, 2011; McGeer and McGeer, 2007).

5. Conclusion and perspectives

Chronic neuroinflammation, demonstrated by the activation of microglia and astrocytes as well as the release of reactive oxygen species and cytokines, has attracted considerable interest in motor and cognitive disorders over

the past decade, not only for its potential role in contributing to neuronal degeneration, but also as a target site for developing potent therapeutics in the future. Recently, flavonoids and LC n-3 PUFA have emerged as potential dietary strategies to reduce the population incidence of dementia and other neurodegenerative disorders. Separately, polyphenols and fish-derived LC n-3 PUFA (DHA and EPA) have been shown to modulate various aspects of brain and cardiovascular functions, and to influence behaviour in both animal and human. As we continue to elucidate the anti-inflammatory mechanisms underlying age-related neurodegenerative diseases, the reductionist strategy in nutrition-cognitive function research has focused on establishing the impact of individual foods, food groups or dietary components. However, as the neural processes involved in cognitive functions are complex and influenced by a number of factors (physical exercise, lifestyle habits, genotype, cardiovascular and metabolic risk factors) and diet component targets are different, a combination of nutritional compounds may be most efficacious. As a framework of balanced dietary strategy, adherence to a Mediterranean diet enriched in fruit, vegetables and unsaturated fatty acids has reported cognitive benefits against dementia (Huhn et al., 2015). More recently, the combination of fish oil LC n-3 PUFA along with vitamin supplements in the Souvenaid® nutraceutical demonstrated cognitive improvement in mild AD patients (Scheltens et al., 2012). In addition to their potential role in neuroinflammation, the antioxidant property of flavonoids may prevent LC n-3 PUFA from peroxidation to which they are particularly sensitive due to their multiple double bonds (Cazzola and Cestaro, 2011) and further supports a synergistic effect of both food compounds. To our knowledge, only one animal study to date investigated the impact of combined flavonoids and fish oil and demonstrated a significantly greater anti-amyloidogenic effect, relative to either component fed separately in AD transgenic mice (Giunta et al., 2010). A better understanding of the additive, synergistic, and antagonistic effects of various dietary bioactives in microglia are therefore warranted. Nonetheless, it is worth noting that it is not clear whether the dietary bioactives shown to have anti-inflammatory activity access the brain to interact directly with microglia or other brain cells. While it is biologically plausible that peripheral inflammatory modulation may reflect underlying brain health, further human studies would be required to elucidate whether dietary bioactives can act as anti-inflammatory agents in the CNS. In this perspective, future clinical investigations would pay attention to larger sample sizes and longer follow-up in both healthy volunteers and in clinical conditions associated with a better screening of diet, including diet deficiency, and lifestyle habits (physical exercise, cognitive stimulation and social engagement) at sufficiently early stage or at least before the onset of neurodegenerative impairments (Gillette-Guyonnet et al., 2013). In addition, the use of imaging techniques like positron emission tomography (PET) imaging which can measure the *in vivo* changes in microglial activation (Cagnin et al., 2007) could support the relatively consistent

epidemiological and mechanistic evidence obtained so far and provide valuable information on the anti-inflammatory effects of these promising compounds *in vivo*.

Acknowledgements

Funding by the Biotechnology and Biological Sciences Research Council (DV; BB/M004449/1) and INRA, Bordeaux University, Région Aquitaine (SL) are gratefully acknowledged.

Conflict of interest

The authors declare no financial or personal conflict of interest.

Figures caption

Figure 1: Microglia phenotypes and inflammaging.

Whilst M1 cells have cytotoxic properties, express proinflammatory cytokines and are characterized by the so-called sickness behabiour in response to an immune stimulus, M2a cells are involved in resolution, repair and regeneration and express anti-inflammatory cytokines to deactivate the M1 microglial phenotype. In addition, when challenged with either immune stimuli or a stress, aged animals clearly mount an exaggerated neuroinflammatory response (priming/sensitization). Inflammaging is characterised by microglia senescence and the production of low-grade proinflammatory cytokines at the expense of anti-inflammatory factors at the periphery and in the brain. In addition to producing proinflammatory cytokines, senescent microglia also express lipofuscin granules, higher levels of CD86, major histocompatibility complex II (MHC II), toll-like receptors (TLRs) and complement receptor 3 (CR3/CD11b) and display a decreased number and complexity of processes as described in activated microglia. Sustained inflammation and inflammaging are responsible for the development of neurodegenerative and neuropsychiatric disorders.

Figure 2: Flavonoids and LC n-3 PUFA are potent regulators of neuroinflammatory processes.

Both flavonoids and LC n-3 PUFA cross the blood brain barrier and exert neuroprotective effects by suppressing the activation of microglia through the down-regulation of cytokine expression and the modulation of signalling pathways involved in the resolution of inflammation. LC n-3 PUFA also yield protective influence indirectly, through the synthesis of bioactive derivates with pro-resolutive activities (resolvins and protectins). IDO, indoleamine 2,3-dioxygenase; GTP-CH1, guanosine triphosphate cyclohydrolase I; ROS, reactive oxygen species; RvD1-5, resolvins D1-D5; TLR, Toll-like receptor; NOD, nucleotide-binding oligomerization domain protein, a family member of NOD-like receptor; ALX/FPR2, lipoxin A4 receptor/formyl peptide receptor 2; JNK, c-Jun N-terminal kinase; AA, arachidonic acid; cPLA2, cytosolic phospholipase A2; NO, nitric oxide; NOS, nitric oxide synthase.

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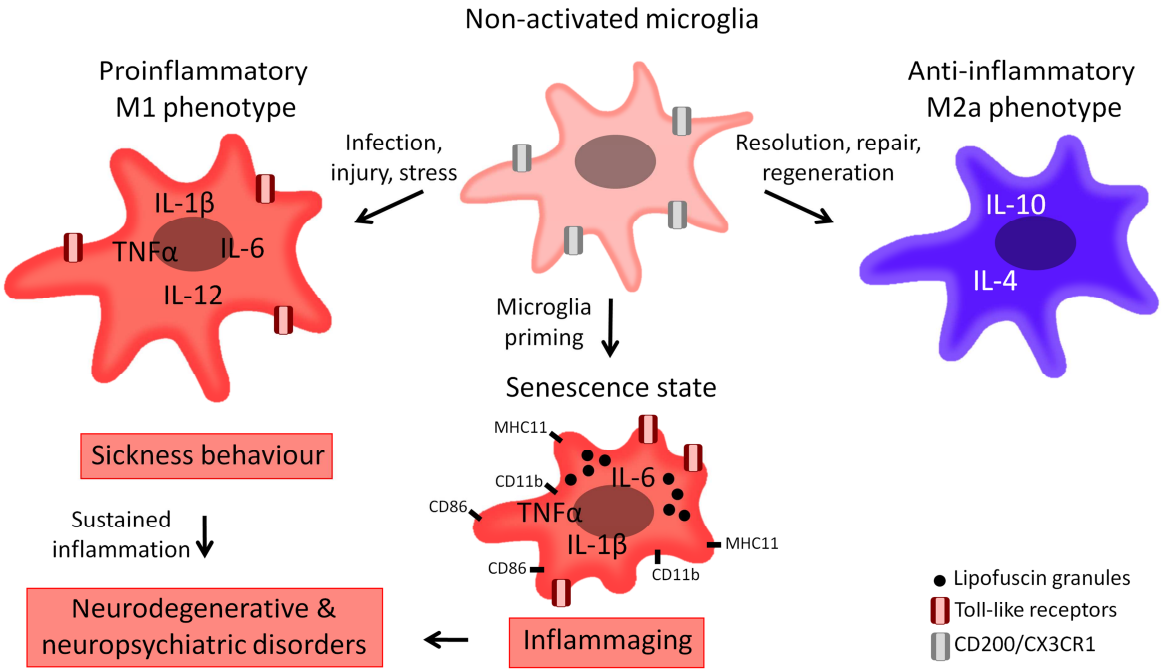

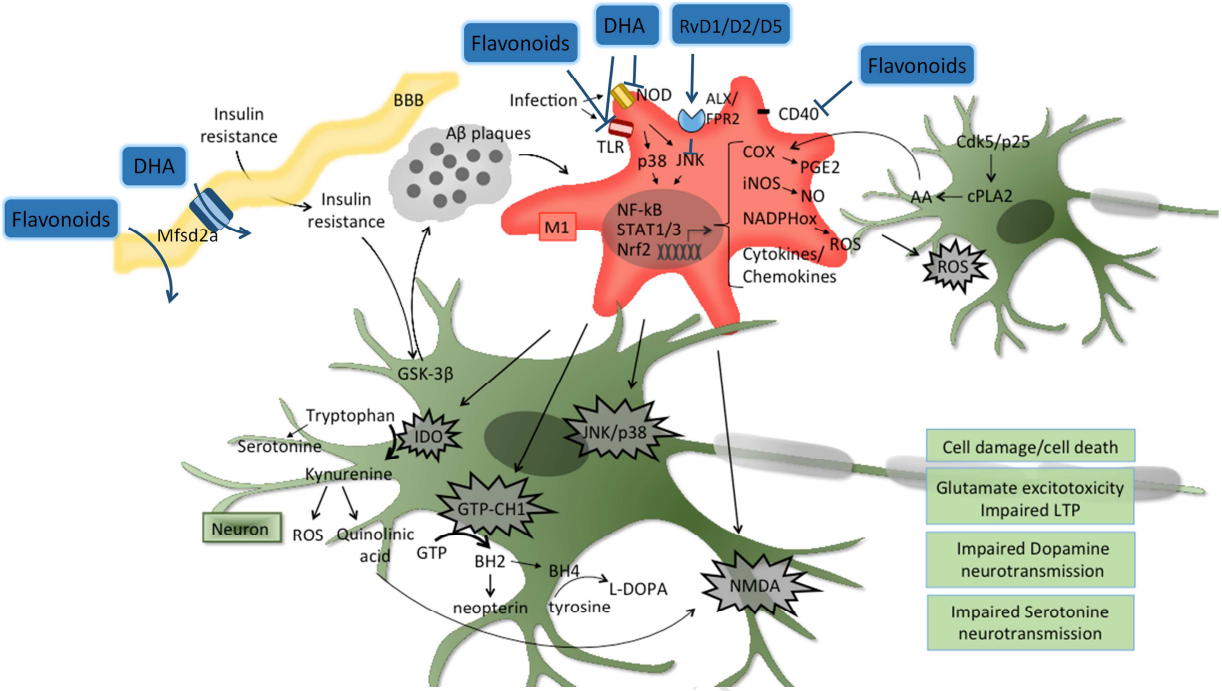

Highlights

- Activated microglia contributes to chronic neuroinflammation and cognitive deficits
- Microglia can become dysregulated during ageing and prone to proinflammatory stimuli
- Dietary flavonoids and n-3 PUFA are potent anti-inflammatory bioactives
- Flavonoids and n-3 PUFA resolve inflammation through several signalling pathways