# Neuroinflammation, Microglia and Mast Cells in the Pathophysiology of Neurocognitive Disorders: A Review

Stephen D. Skaper*, Laura Facci and Pietro Giusti

*Department of Pharmaceutical and Pharmacological Sciences, University of Padua, 35131 Padua, Italy*

**Abstract:** Cells of the immune system and the central nervous system are capable of interacting with each other. The former cell populations respond to infection, tissue injury and trauma by releasing substances capable of provoking an inflammatory reaction. Inflammation is now recognized as a key feature in nervous system pathologies such as chronic pain, neurodegenerative diseases, stroke, spinal cord injury, and neuropsychiatric disorders such as anxiety/depression and schizophrenia. Neuroinflammation may also raise the brain's sensitivity to stress, thereby effecting stress-related neuropsychiatric disorders like anxiety or depression. The cytokine network plays a large part in how immune system cells influence the central nervous system. Further, inflammation resulting from activation of innate immune system cells in the periphery can impact on central nervous system behaviors, such as depression and cognitive performance. In this review, we will present the reader with the current state of knowledge which implicates both microglia and mast cells, two of the principle innate immune cell populations, in neuroinflammation. Further, we shall make the case that dysregulation of microglia and mast cells may impact cognitive performance and, even more importantly, how their cell-cell interactions can work to not only promote but also amplify neuroinflammation. Finally, we will use this information to provide a starting point to propose therapeutic approaches based upon naturally-occurring lipid signaling molecules.

**Keywords:** Alzheimer disease, astrocytes, cognition, lipid signaling molecules, mast cells, microglia, mood disorders, neuroinflammation.

## KEY POINTS

- Inflammation is a key element in the pathobiology of neurodegenerative diseases and neuropsychiatric disorders such as anxiety/depression.
- Immune system-derived non-neuronal cells (microglia, mast cells) are key players in systemic and central neuroinflammtion.
- Dysregulation of microglia and mast cells may impact cognitive performance.
- Modulation of microglia and mast cells by endogenous lipid signaling molecules can offer a novel therapeutic strategy for neurocognitive decline associated with depression and Alzheimer disease.

## INTRODUCTION

The extensive communication that exists between the immune system and the central nervous system (CNS) represents one of the more fundamental advances in neuroscience [1]. Infection, tissue injury and trauma can lead to the release of substances which activate the innate immune system, leading to an inflammatory reaction. Inflammation is per se a protective response by the organism aimed at removing injurious stimuli and initiating the healing process. When protracted, however, inflammation surpasses the bounds of physiological control and becomes destructive. Neuroinflammatory conditions are characterized by immune responses compromising components of the nervous system (Karolinska Institute, 2013, www.ki.se). Inflammation is now seen as a key element in the pathobiology of chronic pain, neurodegenerative diseases, stroke, spinal cord injury, neuropsychiatric disorders [2-6] and possibly autism spectrum disorder [7]. Neuro- and immune signal molecules (e.g. hormones, neurotransmitters/ peptides, cytokines) together with their receptors at part of the same superfamily which facilitates this mutual neuroimmune communication [1]. Neuroinflammation may also raise the brain's sensitivity to stress. A recent study by Rivat and colleagues [8] demonstrated that chronic stress induces transient spinal neuroinflammation, triggering sensory hypersensitivity and long-lasting anxiety-induced hyperalgesia. Indeed, it is becoming increasingly clear that inflammation represents a common mechanism of disease - especially when one realizes the relationship that emerges between inflammation and the development of cardiovascular disease and diabetes [9].

An ever-expanding body of evidence links inflammation with the risk of depression. People with inflammatory diseases such as multiple sclerosis (MS) [10], cardiovascular disease, rheumatoid arthritis [11] and psoriasis have elevated rates of depression. A comparison of non-depressed individuals to patients with major depression (irrespective of health status) shows the depressed group to exhibit essential features of inflammation, such as elevated peripheral blood and cerebrospinal fluid (CSF) levels of innate immune system-derived inflammatory cytokines tumor necrosis factor alpha (TNF-α) and interleukin-6 (IL-6) [12] (the latter being one of the more reliable peripheral biomarkers in major depression), along with elevations in peripheral blood levels of acute phase

*Address correspondence to this author at the Department of Pharmaceutical and Pharmacological Sciences, University of Padua, Largo "E. Meneghetti" 2, 35131 Padua, Italy; Tel: 0039-049-8275084; Fax: 0039-049-8275093; E-mail: stephen.skaper@unipd.it

1996-3181/14 $58.00+.00 

proteins, chemokines (e.g. monocyte chemoattractant protein (MCP)-1), adhesion molecules, and other inflammatory mediators [13]. Administration of inflammatory cytokines to healthy individuals leads to depression [14]. Interferon-alpha (IFNα) treatment of non-depressed hepatitis C patients consistently induces moderate to severe symptoms of depression in 20% to 50% of patients [15-17], along with increases in serum IL-6 levels and cerebrospinal fluid concentrations of IL-6 and MCP-1 [18]. Further, rats subjected to chronic stress showed elevated serum levels of IL-6 and TNF-α [19]. IL-6-deficient mice reportedly exhibit resistance to stress-induced development of depression-like behaviors [20], although central administration of IL-6 can elicit a depressive-like phenotype in mice [21]. The above observations taken on added importance when one considers that these cytokines can influence a plethora of pathophysiologic processes relevant to depression, including neurotransmitter metabolism, neuroendocrine function, synaptic plasticity, and regional brain activity [13, 14].

The association of cognitive dysfunction with neuroinflammatory processes is not limited to depression, but can be found also in Alzheimer disease/dementia (Table **1**). This review will focus on two key innate immune cell populations involved in neuroinflammation, namely microglia and mast cells, evidence pointing to their involvement in cognitive dysfunction associated with both depression and Alzheimer disease, the role that microglia-mast cell interactions may play in promoting neuroinflammation and, finally, how this knowledge can be leveraged to identify innovative therapeutic approaches for neuroinflammation and neurocognitive disorders.

## MICROGLIA, MAST CELLS AND NEUROCOGNITIVE (DYS)FUNCTION

### Depression

Inflammation is a complex and coordinated response of the body to a range of noxious stimuli. These can include not only infectious agents, but can also other external or internal cues, including components of damaged or diseased tissues. Medical conditions associated with chronic inflammatory and immunological abnormalities, such as obesity, diabetes, rheumatoid arthritis, and MS are risk factors for depression [22-24].

It is important to understand that a systemic inflammatory challenge can provoke immune cell-mediated CNS

**Table 1. Neuroinflammatory – immune cell association with depression and neurocognitive disorder*.**

| Depression | Action | References |
|---|---|---|
| Microglia | Traumatic brain injury is associated with a higher incidence of depression and microglial cell activation.<br>Peripheral lipopolysaccharide (LPS) challenge provokes a more robust inflammatory cytokine response in primed microglia of traumatic brain injury mice and is associated with onset of depressive-like behavior.<br>Microglia dysregulation is associated with psychiatric disease. | [39-41] |
| Mast Cells | Patients with mastocytosis exhibit cognitive impairment and collelations to depression; masitinib, a protein tyrosine kinase inhibitor with a specific action on mast cells improves depression outcome. | [57, 61, 155] |
| LPS | Peripherally administered LPS raises brain levels of pro-inflammatory cytokines and causes depression-like symptoms. | [27-29] |
| Pro-Inflammatory Cytokines | Chronic exposure leads to depression. | [14-17, 21, 156] |
| Central Inflammation | Excessive brain inflammatory cytokine response is associated with cognitive dysfunction and depressive-like behavior. | [33-35] |
| Obesity | Obesity-associated inflammatory priming renders vulnerable to immune-mediated depressive symptoms. | [36] |
| **Neurocognitive Disorder*** | | |
| Microglia | Systemic inflammation leads to their activation in the brain and neurodegenerative responses;<br>Neuroinflammation mediated by activated microglial cytokines implicated in the pathogenesis of radiation-induced cognitive impairment. | [95, 157] |
| Mast Cells | A chymotrypsin-like mast cell found in Alzheimer disease brain. | [158] |
| Aging Brain | Microglia are primed to be activated and resistant to regulation,<br>Astrocytes in the aging brain express characteristics of senescence-associated secretory phenotype. | [159, 160] |
| Mild Peripheral Inflammation in Humans | Gives rise to associated functional impairment in the form of reduced spatial memory performance;<br>suggests a mechanism for the observed epidemiologic link between inflammation and risk of age-related cognitive decline and progression of neurodegenerative disorders including Alzheimer disease. | [161] |
| Chronic Inflammation | Accelerates age-related cognitive impairment. | [162] |
| | Neuroinflammation mediated by activated microglial cytokines has been implicated in the pathogenesis of radiation-induced cognitive impairment. | [95] |

*In relation to Alzheimer disease.

inflammation - and depression. For example, chronic functional bowel syndrome is characterized by enhanced gut-brain axis dysfunction, neuroinflammation, cognitive impairment, and vulnerability to dementia [25]. Lipopolysaccharide (LPS) (endotoxin derived from the cell walls of Gram-negative bacteria) stimulates pro-inflammatory cytokine (IL-1β, TNF-α, IL-6) release from monocytes and macrophages [26] and triggers an intracellular inflammatory cascade which involves the stress-activated and mitogen-activated protein kinases. Indeed, peripherally administered LPS raises brain levels of pro-inflammatory cytokines and causes depression-like symptoms [27-29]. How are such signals conveyed from the periphery to the CNS? Upon activation, peripheral innate immune cells secret inflammatory cytokines that harness neural [30] and blood-brain barrier (BBB) pathways [31] to signal the CNS – thereby inducing CNS macrophages and microglia to produce the same cytokines [32]. Excessive brain inflammatory cytokine response is associated with cognitive dysfunction [33, 34] and depressive-like behavior [35].

Prolonged exposure of mice to a western diet (consisting of palatable energy-dense food) altered LPS-induced depressive-like behavior and worsened hippocampal and hypothalamic pro-inflammatory cytokine expression and activity of the brain's tryptophan-catabolizing enzyme indoleamine 2,3-dioxygenase [36], the latter being strongly associated with depression [35, 37]. Obesity is associated with a high prevalence of mood symptoms and cognitive dysfunctions, as well as peripheral low-grade inflammation and increased susceptibility to immune-mediated diseases [38].

Microglia, the major (but not only) innate immune cell population in the CNS, are key players in the development of depression. For instance, traumatic brain injury (TBI) is associated with a higher incidence of depression [39]. Utilizing a fluid percussion model of TBI in mice, Fenn *et al*. [40] observed 30 days post-TBI a population of microglia expressing major histocompatibility complex $II^+$ (also called human leukocyte antigen, a molecular signature of microglia activation), which serves as an antigen presenter to T helper cells. Peripheral LPS challenge provoked a more robust inflammatory cytokine response in primed microglia of TBI mice compared with controls; this late LPS-induced microglia reactivity post-TBI was associated with onset of depressive-like behavior [40]. See Frick *et al*. [41] for a recent review on microglial dysregulation in psychiatric disease.

Peripheral inflammation induces transmigration of interleukin-1β (IL-1β)-expressing neutrophils to the brain [42]. Mice treated with LPS developed despair-like and asocial behaviors, which were abolished by giving an anti-polymorphonuclear antibody. Increasing endogenous levels of the energy-regulating hormone leptin during obesity exacerbated the behavioral changes [42]. These authors proposed a role for peripheral neutrophils in conveying inflammatory signals to the brain, as a function of the organism's energy status.

The mast cell (Fig. **1**) represents today an underappreciated peripheral immune signaling link to the brain where inflammation is concerned. Mast cells, which belong to the innate immune system and share similarities with circulating basophil granulocytes, derive from different bone marrow precursor cells [43]. Mast cells – in contradistinction to basophils – circulate as immature cells until reaching their chosen tissue site to settle. This behavior probably determines their particular characteristics. Mast cells are found in most tissues close to blood vessels, and near surfaces in contact with the environment [44]. They take part in innate host defense reactions, are located in peripheral tissues innervated by small diameter sensory nerve fibers and within the endoneural compartment of peripheral nerves, and in cerebral blood vessel meninges. During development mast cells enter the brain *via* penetrating blood vessels, with which they remain associated [45]. Mast cells are normally able to move through the BBB [46] and also traverse the blood–spinal cord barrier and BBB when the latter are compromised by disease. Mast cells are capable of phagocytosis and antigen presentation, and can modulate the adaptive immune response, as well (Box **1**).

The spectrum of mast cell mediators is vast, encompassing biogenic amines, cytokines, enzymes, lipid metabolites, ATP, neuropeptides, growth factors and nitric oxide [47] (Table **2**). Because mast cells are heterogeneous in nature, no single one makes all of these. Given their immune regulatory role, mast cells take part in IgE switching by B cells [48], and the release of chemoattractants that recruit eosinophils [49] and monocytes [50]. In disease states involving autoimmune demyelination, increased numbers of mast cells per se and also cells in a state of degranulation can be found within the CNS [51]. Activated mast cells can effect demyelination [52] and induce apoptotic death of oligodendrocytes [53]. It has been suggested that brain mast cells might provide a 'bridge' between the immune system and anxiety-like behavior [54].

Are mast cells implicated in depression? Consider mastocytosis, which is characterized by mast cell accumulation in peripheral organs [55]. Patients with mastocytosis exhibit psychopathological manifestations such as cognitive impairment; depression appears to be the most common complaint among these patients and ranges from 40% to 70% [56, 57] - as compared to about 7% in the general population [58]. Hermine *et al*. [56] reported a dissociation between the physical effects of mastocytosis and depression, suggesting that core aspects of depression are a fallout from the actual physical involvement of the disease [56]. A systemic brain involvement mediated by mast cell mediators could, in principle, account for this high prevalence of depression. Mast cells have been implicated in mechanisms related to the regulation of emotion [54]. A possible link between depression in mastocytosis and mast cell activation is suggested by preclinical/clinical studies showing that masitinib, a protein tyrosine kinase inhibitor with a specific action on mast cells was efficacious in treating cutaneous mastocytosis in dogs and in improving recovery from depression associated with mastocytosis [59-61].

**Neurocognitive Disorder and Alzheimer Disease**

A decline in cognitive functions, including memory, is part of the aging process across mammalian species, including man. So-called 'cognitive aging' affects more than

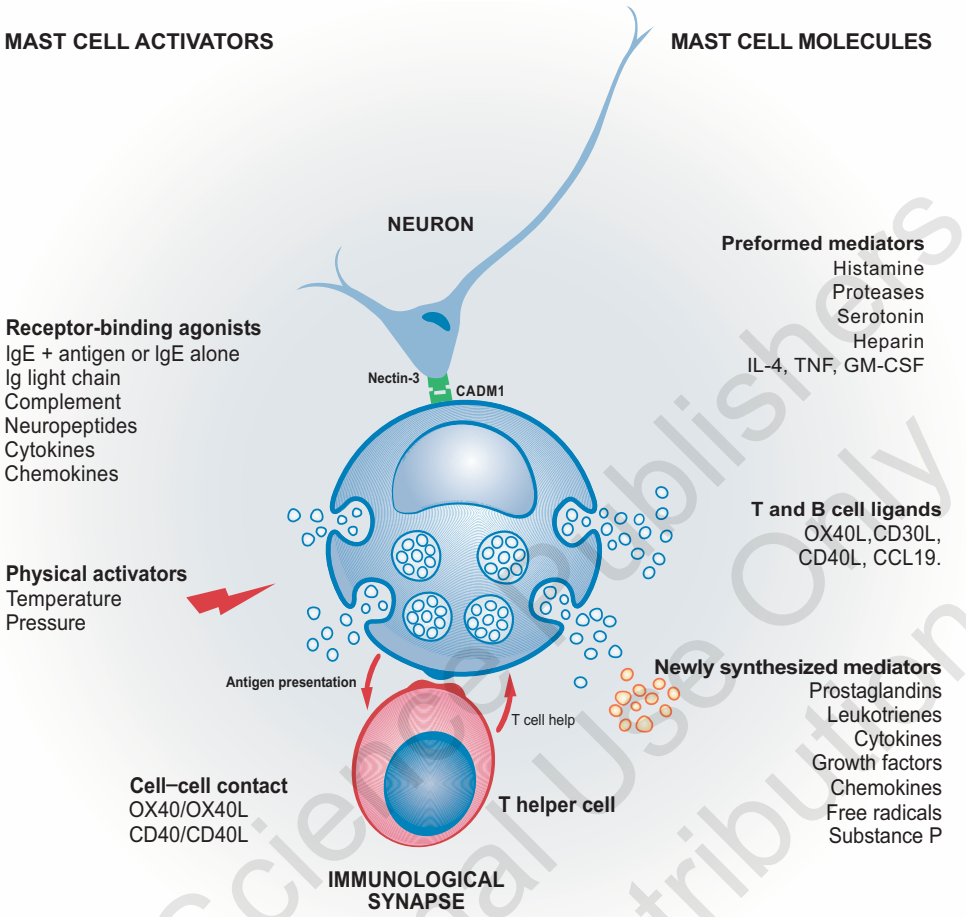


**Fig. (1).** The mast cell: a 'jack-of-all trades' immune cell. Depiction of the many mast cell activators and molecules elaborated by mast cells. It is important to keep in mind that mast cell activation involves both the rapid release of preformed agents like tumor necrosis factor (TNF), interleukin-4 (IL-4) and GM-CSF (granulocyte macrophage colony-stimulating factor) followed by a slower de novo synthesis of cytokines (TNF), chemokines, and growth factors like nerve growth factor. The cell adhesion molecule 1 (CADM1) on mast cells promotes interaction with dorsal root ganglion neurites by heterophilic binding to nectin-3 [163]. Intercellular contacts between T cells and antigen-presenting cells (such as mast cells) initiate T-cell signaling, whereby T-cell surface receptors recognize antigens bound to major histocompatibility complex molecules on the antigen-presenting cell. This process (which also engages adhesion receptors) creates a specialized junction between the two cell types – the so-called immunological synapse [164], which mediates delivery of effector molecules (*via* microvesicles) and intercellular signals across this cleft [164].

50% of people over 60 years of age [62]. Age-related cognitive decline (or impairment) is more likely to be related to alterations in synaptic connectivity rather than neuronal cell loss [63] - an important distinguishing feature compared to pathological conditions such as Alzheimer disease (AD) [64] and other chronic neurodegenerative disorders. The distinction between elderly individuals that experience a reduction in cognitive ability that is not a consequence of neurodegenerative disease and amnesic mild cognitive impairment is important, as the latter is associated with markers of brain atrophy and often a prelude to AD. Today it is probably more correct to speak of 'Mild Neurocognitive Disorder' (Mild-NCD) rather than mild cognitive impairment, as defined in the Fifth edition of *Diagnostic and Statistical Manual of Mental Disorders* (DSM-V, American Psychiatric Association, May 2013). While DSM-IV (published 20 years ago) defined mild cognitive impairment as a clinical situation of cognitive decline in rather generic terms, DSM-V places emphasis on the relationship between the clinical syndrome of cognitive decline and underlying cellular/molecular mechanisms. Mild-NCD is an important risk factor for Major-NCD [65].

Normal aging is associated also with a glial shift toward an activated phenotype, perhaps reflective of an increased inflammatory signaling. At face value this might be generally beneficial to the CNS, since it tends to minimize further injury while contributing to repair of damaged tissue which may be part of the aging process. In contrast, *pathological* gliosis and inflammation are now implicated in the severe cognitive dysfunction seen in neurodegenerative disease states such as AD, vascular dementia, TBI, chronic stress and direct inflammatory stimulation (e.g. LPS, as

**Box 1. Mast cell flash card.**

**Origin and Classification**:

- First described by Paul Ehrlich in 1878 on the basis of their unique staining characteristics and large cytoplasmic granules.
- Very close to basophil granulocytes in blood; current evidence suggests that mast cells are generated by different precursor cells in the bone marrow.
- Thought to originate from bone marrow precursors expressing CD34; a distinct subset of mast cells can also be induced upon host responses to inflammation.
- The hematopoietic lineage development of tissue mast cells is unique compared to other myeloid-derived cells because it is early lineage progenitors, undetectable by histochemistry, that leave the bone marrow to enter the circulation. These immature lineage mast cells immediately undergo transendothelial recruitment into peripheral tissues wherein the appearance of secretory granules with a particular protease phenotype is regulated by the peripheral tissue.
- Classified by their species-dependent protease constitution rather than location.
- Present in most tissues in the vicinity of blood vessels, and are especially prominent near the boundaries between the body's external environment and the internal milieu, such as the skin, mucosa of the lungs and digestive tract, as well as in the mouth, conjunctiva and nose.
- Mast cells are also found within the nervous system, including meninges, brain parenchyma and nerve.

**Physiology**:

- Play a key role in innate and acquired immunity.
- Upon activation rapidly release granules into the interstitium.
- Degranulation is caused by direct injury (e.g. physical or chemical), cross-linking of high-affinity FcεR1 IgE receptors or by activated complement proteins.
- Capable of elaborating a vast array of important cytokines and other inflammatory mediators.
- Express multiple "pattern recognition receptors" thought to be involved in recognizing broad classes of pathogens.
- Granules carry a variety of bioactive chemicals, proteoglycans, serine proteases, neuropeptides; can be transferred to adjacent cells of the immune system and neurons *via* transgranulation and their pseudopodia.

**Role in Disease**:

- Allergic reactions.
- Anaphylactic shock.
- Neuropathic and inflammatory pain.
- Acute and chronic neurodegenerative disorders.

[Adapted from: Skaper SD, Facci L, Giusti P. Mast cells, glia and neuroinflammation: partners in crime? Immunology 2013; 141(3): 314-27 (Box **1**)].

discussed earlier) [66-70]. Acute cognitive impairment (i.e., delirium) frequently results from infections in the absence of CNS involvement. Activation of the peripheral innate immune system induces microglia (together with macroglia and infiltrating leukocytes) to elaborate inflammatory cytokines that are responsible for behavioral deficits. Peripheral innate immune system activation in aged mice can exacerbate neuroinflammation and prolonged sickness behaviour [71], suggesting that dysregulation between the peripheral and central innate immune systems may have a role in the severe behavioral deficits that often occur in older adults with systemic infections. Drebrin A, a neuron-specific F-actin-binding protein found only in dendrites, is especially concentrated in dendritic spines receiving excitatory inputs. This protein is reportedly decreased in post-mortem temporal regions obtained from severe and mildly cognitively impaired patients [72]. A reduction in drebrin has been claimed to correlate with cognitive impairment in AD patients [72, 73].

Microglia play a role in synaptic remodeling and plasticity in the healthy brain [74], and dynamic interactions between microglia and synaptic elements in the mature CNS have been revealed in imaging studies [75]. One mechanism by which microglia could interact with developing synapses is the classical complement cascade, whose components C1q and C3 in immature synapses are necessary for the developmental pruning of retinogeniculate synapses [76]. A follow-up study by Schafer *et al*. [77] showed that microglia engulf presynaptic inputs during peak retinogeniculate pruning, a process dependent upon neural activity and the microglia-specific complement receptor 3(CR3)/C3. Inflammatory neuropathologies are often associated with hypoxia caused by a reduced/altered neurovascular coupling and cerebral blood flow [78]. Hypoxia, acting in concert with neuroinflammation can worsen damage and provoke cognitive decline in such conditions [78]. In the peripheral immune system, inflammation and hypoxia share similar downstream pathways to produce an enhanced inflammatory reaction [79]. Building on these earlier findings, Zhang *et al*. [80] investigated whether hypoxia and an inflammatory stimulus act synergistically to modulate synaptic function in a microglial CR3-dependent mechanism. These authors showed combining hypoxia and an inflammatory stimulus (LPS) synergized to trigger long-term synaptic depression dependent on microglial CR3 activation, NADPH oxidase, and internalization of glutamatergic α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors. This type of long-term depression was suggested to contribute to memory impairments and synaptic disruptions in neuroinflammation-related brain disorders [80].

Alzheimer disease, the principal cause of senile dementia, is characterized by the presence of extracellular senile plaques of amyloid β-peptide (Aβ) and intracellular neurofibrillary tangles of hyperphosphorylated tau protein in brain [81], along with signs of activated microglia and reactive astrocytes, often associated with Aβ deposits [82, 83]. In AD, activated microglia can clear toxic Aβ assemblies and secreting neurotrophic factors [84]. Phagocytosis of aggregated Aβ by microglia may be beneficial; however, their protracted activation leads to release of synaptotoxic/neurotoxic pro-inflammatory cytokines, chemokines, and reactive oxygen/nitrogen species [82, 84]. In a transgenic mouse AD model inhibition of microglial activation protected hippocampal neurogenesis and improved cognitive deficits [85]. The amyloid hypothesis of AD posits that pathogenesis is initiated by amyloid deposition. Although initially formulated on the perceived deleterious effects of senile plaques, AD is now viewed by many as a disease of synaptic toxicity, in which soluble oligomeric forms of Aβ cause synapse loss and consequent cognitive disruption [86]. An experimental therapeutic (MW-151) which modulates glia biological responses in a mouse transgenic AD model attenuated synaptic dysfunction [87].

**Table 2. Mast cell mediators.**

| Biogenic Amines | Biogenic Amines (Histamine (2-5 pg/Cell), Serotonin) |
|---|---|
| Cytokines | Interleukins 1-6 |
| | Leukemia Inhibitory Factor |
| | Tumour Necrosis Factor-α |
| | Interferon-γ |
| | Transforming Growth Factor-β |
| | Granulocyte-Microphage Colony-Stimulating Factor |
| Enzymes | Acid Hydrolases |
| | Phospholipases |
| | Rat Mast-Cell Protease I and II |
| | Serine Proteases (Chymase, Trypase) |
| Lipid Metabolites | Prostaglandin D2 |
| | Leukotriene C4 |
| | Platelet-Activating Factor |
| | Thromboxane |
| T and B Cell Ligands | PD-L1 |
| | OX40L |
| | CD30L |
| | CD40L |
| | CCl19 |
| Other Bioactive Molecules | Neuropeptides (e.g. Vasoactive Intestinal Peptide, Substance P) |
| | Proteoglycans, Mainly Heparin (Active as an Anticoagulant) |
| | Nerve Growth Factor |
| | ATP |
| | Nitric Oxide |

Cognitive decline has also been associated with surgery [88]. Postoperative cognitive dysfunction (POCD) involves a wide range of cognitive functions including working and long-term memory, information processing, attention and cognitive flexibility. Cognitive function often returns to normal within a matter of weeks, although in some patients cognitive decline remains [89]. Advanced age is the main risk factor for POCD [90], and inflammation may play a key role in the disease process [90]. Surgical trauma provokes a local inflammation which is paralleled by a rise in systemic inflammatory mediators [91], the latter influencing inflammatory processes in the brain, microglial cell activation and concurrent production of pro-inflammatory cytokines [91]. An association between neuroinflammation and impaired cognitive functioning could, conceivably, underlie the development of POCD [92, 93]. In line with the age factor for POCD, aging is tied in with an exacerbated inflammatory response [92, 93].

Mild cognitive impairment is a documented consequence of whole brain radiation therapy that affects almost 50% of long-term brain tumor survivors [94]. It typically manifests more than 6 months after radiation exposure. Neuroinflammation mediated by microglial-derived cytokines is implicated in the pathogenesis of radiation-induced cognitive impairment in animal models, which includes disruption of neurogenesis and activity-induced gene expression in the hippocampus. Inhibition of microglia-mediated neuroinflammation mitigates radiation-induced cognitive impairment [95].

A fascinating aspect of glial and mast cell involvement in neuroinflammation is the potential for these two cell populations to 'speak' with each other. This is perhaps not all that surprising, given their frequent proximity at sites of neuroinflammation. The literature in support of this view continues to mount, and will only be briefly summarized here (see [96] for a more detailed discussion). Toll-like receptors (TLRs) represent a major class of pathogen-associated molecular patterns, which are molecules associated with groups of pathogens that are recognized by cells of the innate immune system. Ligand binding to TLR2/TLR4 on mast cells triggers cytokine release which recruits immune cells to the site(s) of injury, while microglial cell recruitment depends on signaling pathways involving TLR2/TLR4. Activation of mast cells up-regulates chemokine expression, including CCL5/RANTES; the latter are capable of inducing a pro-inflammatory profile in

microglia. In turn, IL-6 and CCL5 released from microglia may affect mast cell expression of TLR2/TLR4. ATP released into the extracellular milieu following damage to cells/tissues is a potent microglial cell stimulant, and may act in an autocrine/paracrine fashion on mast cells. ATP released from one single mast cell (e.g. FcεR1 cross-linking, stress) can traverse several hundred micrometers to trigger a rise in $Ca^{2+}$ in neighboring cells [97]. Further, ATP binding to purinergic P2 receptors may provoke IL-33 release from microglia already activated with pathogen-associated molecular patterns *via* TLRs [98]. IL-33 induces mast cell secretion of IL-6, IL-13 and CCL2 which, in turn, modulates microglial cell activity. Mast cell tryptase cleaves and activates microglial cell proteinase-activated receptor 2 (leading to purinergic $P2X_4$ receptor up-regulation) [99], while IL-6 and TNF-α from microglia can up-regulate mast cell expression of proteinase-activated receptor 2, thereby activating mast cells and TNF-α release [100]. The complement system appears to participate in this bi-directional network, as well: the receptor for chemoattractant C5a is up-regulated on reactive astrocytes and microglia in inflamed CNS tissue [101]: Neuroinflammation causes C5a peptide release [102]; there is crosstalk between C5a and TLR4; C5a receptor is up-regulated in activated mast cells and is a strong mast cell chemoattractant signal towards C5a peptide. Recent evidence points also to lines of communication between mast cells and astrocytes (CD40L/CD40; binding of CD40 on antigen-presenting cells to CD40L on T-helper cells activates the former) [103, 104], and microglia and astrocytes (translocator protein, a marker of gliosis) [105]. For an in-depth discussion on mast cell – glia interactions, the reader is referred to a recent review on this topic [96].

## RESOLUTION OF NEUROINFLAMMATION: DOES THE BEGINNING PROGRAM END? A THERAPEUTIC PERSPECTIVE

Natural mechanisms with the capacity for self-defense against inflammation are known to exist. A number of molecules take part in these endogenous protective mechanisms, being activated by tissue damage or stimulation of inflammatory responses. Chronic inflammatory processes may be counteracted by a program of resolution that includes the production of lipid mediators with the capacity to turn off inflammation [106]. Such inflammatory conditions may lower the levels or actions of these 'resolving' molecules [107]. Harnessing one or more of these lipid mediators can be one way "*to commandeer nature's own anti-inflammatory mechanisms and induce a "dominant" program of resolution*" [108]. Consider, for example, the N-acylethanolamines (NAEs). Among these fatty acid amides are the endocannabinoid N-arachidonoylethanolamine (anandamide) and congeners N-stearoylethanolamine, N-oleoylethanolamine and N-palmitoylethanolamine (PEA, or palmitoylethanolamide) [109]. PEA and (and other members) are formed from N-acylated phosphatidylethanolamine (NAPE) by diverse enzymatic pathways [110], involving a membrane-associated NAPE-phospholipase D which yields the respective NAE and phosphatidic acid [111] (Fig. **2**). This enzyme converts N-palmitoyl-phosphatidylethanolamine into PEA. In the mammalian brain, NAEs are broken down into the corresponding fatty acid and ethanolamine by both: (i) fatty acid amide hydrolase (FAAH) in the endoplasmic reticulum [112]; (ii) lysosomal NAE-hydrolyzing acid amidase (NAAA) [113] (Fig. **2**). NAAA is found mainly in macrophages, where it hydrolyses NAEs with less than 18 carbon atoms (e.g. PEA). FAAH, on the other hand hydrolyzes all these NAEs.

Endogenous lipid signaling molecules like PEA may function to maintain cellular homeostasis against external stressors leading, for example, to inflammation [114, 115]. Microglia and mast cells produce/hydrolyze PEA [116, 117], PEA moderates mast cell activation [118] and controls microglia behaviors [119, 120]. Tissue levels of PEA are raised in those brain areas involved in nociception and in spinal cord following induction of neuropathic pain [121], and in other situations associated with pain development [119, 122, 123]. Taken together, these observations posit that PEA maintains cellular homeostatic balance by mediating the resolution of inflammatory processes. By extension, one might ask if exogenous administration of PEA may be of therapeutic benefit. An ever-growing number of studies, both preclinical and clinical support this notion. The reader is referred to several recent reviews for a more detailed discussion of these findings [124, 125].

Inhibiting PEA degradation by targeting NAAA may provide a complementary strategy to treat neuroinflammation and its associated consequences such as neurocognitive decline. A growing number of reports on selective NAAA inhibitors have appeared [126-134]; these inhibitors modulate responses induced by inflammatory stimuli *in vivo* and *in vitro* [126,132], and also elevate PEA levels *in vitro* [126]. One particular compound, 1-(2-biphenyl-4-yl)ethylcarbonyl pyrrolidine, reversibly and competitively inhibits NAAA, raises PEA levels in mouse macrophages stimulated with LPS, and reduces levels of inducible nitric oxide synthase and IL-6 mRNAs [131]. The newest NAAA inhibitors claim single-digit nanomolar intracellular activity ($IC_{50}$ = 7 nM) on both the rat and human enzyme [132].

Neurocognitive parameters and PEA effects can be modelled in a pharmacological mouse paradigm of AD, in which intracerebroventricular injection of $A\beta_{25-35}$ peptide impaired spontaneous alternation performances, and spatial and non-spatial memory tasks [135]. Daily subcutaneous administration of PEA starting 3 h after injection of $A\beta_{25-35}$, for 1 or 2 weeks reduced (10 mg/kg PEA) or prevented (30 mg/kg PEA) the amyloid-induced behavioral impairments. However, PEA was ineffective in $A\beta_{25-35}$-injected peroxisome proliferator-activated receptor α (PPARα) null mice. PEA counteracted reactive astrogliosis induced by Aβ [136]. In the mouse neurotoxin (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; MPTP) model of Parkinson disease intraperitoneal administration of PEA reduced MPTP-induced loss of tyrosine hydroxylase-labeled neurons in the substantia nigra pars compacta and microglial/astrocyte activation [137]; PEA also reversed MPTP-associated motor deficits.

There is a growing evidence in support of an association between oxidative stress and mild-NCD [138,139]. Oxidative stress is implicated also in neuropsychological disorders including depression/anxiety [140]. Flavonoids are polyphenolic phytochemicals endowed with potent anti-

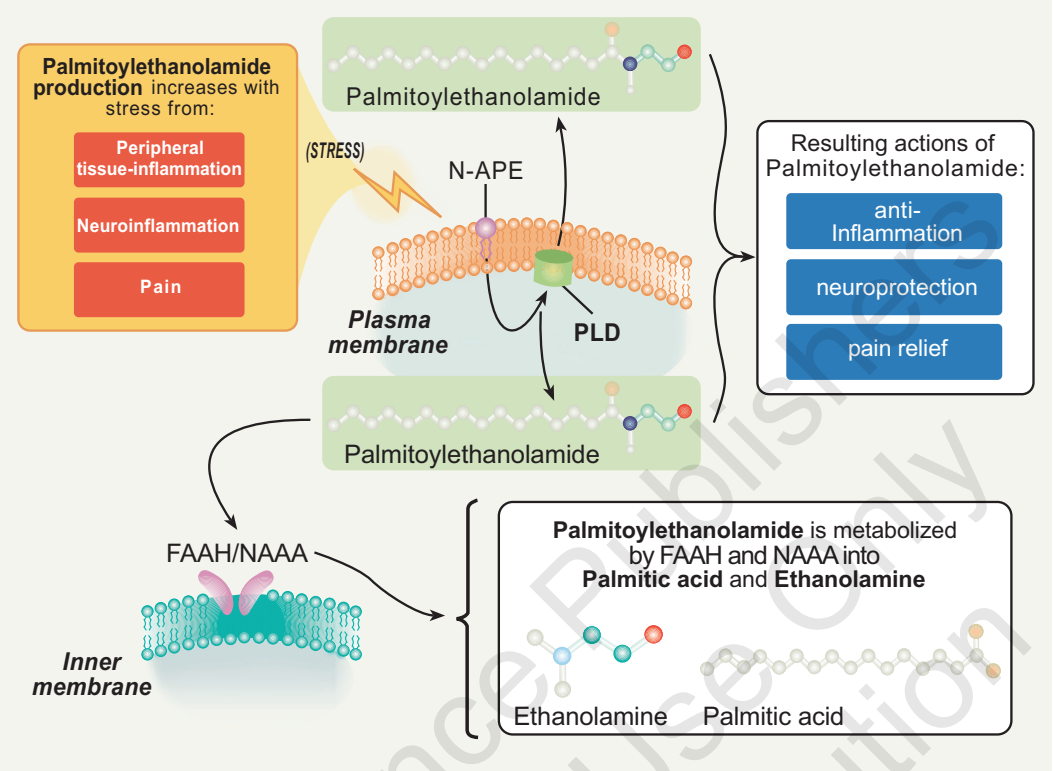


**Fig. (2).** Palmitoylethanolamide synthesis and catabolism. A plasma membrane-associated N-acylated phosphatidylethanolamine-phospholipase D (PLD) converts N-palmitoylphosphatidyl-ethanolamine (N-APE) into palmitoylethanolamide and phosphatidic acid. Palmitoylethanolamide is metabolized to palmitic acid and ethanolamine by fatty acid amide hydrolase (FAAH, which also breaks down other fatty acid amides) and the more selective N-acyl ethanolamine-hydrolyzing acid amidase (NAAA). Tissue levels of palmitoylethanolamide increase in stressful settings such as peripheral tissue inflammation, neuroinflammation and pain. See text for further details. [Reprinted from: Skaper SD, Facci L, Giusti P. Mast cells, glia and neuroinflammation: partners in crime? Immunology 2013; 141(3): 314-27 (Fig. **2**)].

oxidant capacity, and well-described neuroprotective/ anti-inflammatory actions [141, 142]. Amongst the family of flavonoids, luteolin (3',4',5,7-tetrahydroxyflavone) is reported to possess memory-improving [143] and anxiolytic [144] effects. The reported beneficial actions of PEA cannot be ascribed to an antioxidant effect of this NAE, as far as can be ascertained from the literature. Following another approach, studies have been carried out to assess the possibility that a combination of PEA and luteolin is more efficacious than either molecule alone. In a mouse model of anxiety/ depression induced by chronic corticosterone administration, systemic administration of co-ultramicronized PEA/leutolin (10:1 mass ratio) exerted a significant antidepressant effect at doses where PEA alone was ineffective [145]. This PEA/ luteolin composite also promoted hippocampal neurogenesis and dendritic spine maturation, elements which may impact cognition. The co-ultramicronized PEA/leutolin composite, applied to an *ex vivo* model of organotypic hippocampal slices stimulated with $A\beta_{1-42}$ as an AD model normalized expression of inflammatory markers and limited neuronal cell death, where equivalent concentrations of either PEA or luteolin were ineffective [146]. Lastly, co-ultramicronized PEA/luteolin significantly improved motor function and histological alteration in mice with spinal cord injury; neither PEA nor luteolin alone, nor the single administration of PEA and luteolin were effective [147]. That cognitive decline is associated with gene expression changes in the brain, e.g. in AD [148] is reinforced by the recent discovery whereby Crtc1 (cyclic AMP-responsive element binding protein-regulated transcription coactivator-1) regulates expression of multiple proteins involved in synaptic morphology, function, and plasticity, suggests that Crtc1 dysfunction underlies synapse (and hence, cognitive) dysfunction in neurological diseases like AD [149]. It will be interesting in future studies to see if PEA, alone or in concert with luteolin influences gene transcription associated with synaptic function, as well as the reported decrease in expression of synapse-related genes and loss of synapses in major depressive disorder [150].

Signaling lipids such as eicosanoids, phosphoinositides and sphingolipids control a wide array of cellular processes. They include also the NAE family members anandamide, N-oleoylethanolamine, and PEA. These lipid mediators engage nuclear receptors, including PPARs, a subfamily of transcription factors (α-, β/δ- and γ-isoforms). PPARα, which is relatively brain area-selective, modulates antioxidant responses, neurotransmission, neuroinflammation, neurogenesis, and proliferation/differentiation of glia. Lo Verme and colleagues in 2005 [151] were the first to show that PEA - like its analogue N-oleoylethanolamine - acts as an endogenous ligand for PPARα, thereby mediating the anti-inflammatory effects of PEA. PPARα is implicated in PEA neuroprotective and/or anti-inflammatory effects in experimental animal

models of AD [135,136] and Parkinson disease [137]. PEA induced PPARα-dependent allopregnanolone synthesis in astrocytes [152], and pharmacological block of PPARα or its genetic deletion reduced PEA's ability to neutralize $A\beta_{1-42}$-induced reactive gliosis [153]. To quote from Fidaleo *et al*. [154] in their review on PPARα and its lipid ligands: *"This receptor and its endogenous ligands, including palmitoylethanolamide (PEA), are involved in physiological and pathological responses, such as satiety, memory consolidation, and modulation of pain perception. The protective role of PPARα agonists in neurodegenerative diseases and in neuropsychiatric disorders makes manipulation of this pathway highly attractive as therapeutic strategy for neuropathological conditions"*.

## CONCLUSION

Although designed by nature as a cellular response to remove injurious stimuli and initiate the healing process, a protracted state of inflammation overruns the bounds of physiological control to become destructive. Inflammatory effectors, in large part cytokines, derive peripherally from non-neuronal cells of the innate (e.g. mast cells) and adaptive immune systems, as well as microglia (astrocytes) within the CNS. Microglia, the major innate immune cell population in the CNS dominate the inflammatory response during most chronic neurodegenerative diseases. In depression, microglia constitute an important player, as well. While adaptive pathways exist to transduce systemic inflammatory signals to the brain, their activation appears to be deleterious. Indeed, immune dysfunction outside the CNS (systemic inflammation) is now appreciated as part of CNS neuropathology.

As discussed in this review, clinical conditions which express depression and Mild-NCD are frequently associated to neuroinflammation, involving microglia, astrocytes and mast cells. Given that these non-neuronal cell types are able to communicate one with the other, it is not unreasonable to propose the principle of a 'morpho-functional unit' in which these three non-neuronal cell populations act in concert to promote a neuroinflammatory state impinging on the central neuron. This could be a consequence of inadequate non-neuronal cell regulation (excessive and/or persistent endogenous and/or endogenous stimuli) and/or cellular inhibitory capacity. Clearly, a great deal remains to be learned concerning signaling mechanisms that regulate neuroinflammation and its relationship to cognitive performance.

Given that peripheral inflammation has emerged as a modulator of disease progression in depression and neurocognitive decline, one may ask whether or not it can be targetable in new therapeutic approaches, in particular by capitalizing on the body's mechanisms for the resolution of inflammation. In this context, the capability of PEA to modulate protective responses during inflammation has given rise to the hypothesis that this signalling lipid may be part of a complex homeostatic system designed to control the basal threshold of inflammation (modulator of immuno-neural homeostasis). This view is supported by observations that PEA production is up-regulated during inflammatory conditions. Indeed, emerging data that selective inhibition of PEA hydrolysis is anti-inflammatory provides more direct evidence for PEA involvement in the control of inflammation. Perhaps we are missing important therapeutic avenues by studying glia and mast cells separately from each other. In our view, future studies should explore a mast cell role in inflammatory diseases as a network, which will require a critical examination of specific tissue localization, function, and dynamic interaction with endogenous cells.

## REVIEW CRITERIA

A search for original articles published between 2004 and 2014 and focusing on neuroinflammation and cognition was performed in MEDLINE and PubMed. The search terms used were "inflammation", "neuroinflammation", "microglia", "mast cells", "glia", "immune system", "cognition", "depression", "Alzheimer disease", "cytokines", "neuropsychiatric disorders" and "palmitoylethanolamide", alone and in combination. All articles identified were in English language and were full-text papers. We also searched the references' lists of identified articles for additional relevant papers.

## LIST OF ABBREVIATIONS

| | | |
|---|---|---|
| Aβ | = | Amyloid β-Peptide |
| AD | = | Alzheimer Disease |
| BBB | = | Blood-Brain Barrier |
| CNS | = | Central Nervous System |
| FAAH | = | Fatty Acid Amide Hydrolase |
| IFNα | = | Interferon Alpha |
| IL-1β | = | Interleukin-1β |
| IL-6 | = | Interleukin-6 |
| LPS | = | Lipopolysaccharide |
| Mild-NCD | = | 'Mild Neurocognitive Disorder |
| MS | = | Multiple Sclerosis |
| NAAA | = | N-Acyl Ethanolamine-Hydrolysing Acid Amidase |
| NAE | = | N-Acylethanolamines |
| NAPE | = | N-Acylated Phosphatidylethanolamine |
| PEA | = | N-Palmitoylethanolamine |
| POCD | = | Postoperative Cognitive Dysfunction |
| PPARα | = | Peroxisome Proliferator-Activated Receptor α |
| TBI | = | Traumatic Brain Injury |
| TLR | = | Toll-Like Receptor |
| TNF-α | = | Tumor Necrosis Factor Alpha |

## CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

## ACKNOWLEDGEMENTS

This study was supported in part by MIUR, PON 'Ricerca e Competitività 2007 - 2013' project PON01_02512.

## REFERENCES


[1] Wrona D. Neural-immune interactions: an integrative view of the bidirectional relationship between the brain and immune systems. J Neuroimmunol 2006; 172: 38-58.

[2] Ellis A, Bennett DLH. Neuroinflammation and the generation of neuropathic pain. Br J Anesthesiol 2013; 111: 26-37.

[3] Iadecola C, Anrather J. The immunology of stroke: from mechanisms to translation. Nat Med 2011; 17: 796-808.

[4] McGeer PL, McGeer EG. The amyloid cascade-inflammatory hypothesis of Alzheimer disease: implications for therapy. Acta Neuropathol 2013; 126: 479-97.

[5] Karalija A, Novikova LN, Kingham PJ, Wiberg M, Novikov LN. The Effects of N-acetyl-cysteine and acetyl-L-carnitine on neural survival, neuroinflammation and regeneration following spinal cord injury. Neuroscience 2014; 269: 143-51.

[6] Miller AH, Maletic V, Raison CL. Inflammation and its discontents: the role of cytokines in the pathophysiology of major depression. Biol Psychiatry 2009; 65: 732-41.

[7] Noriega DB, Savelkoul HF. Immune dysregulation in autism spectrum disorder. Eur J Pediatr 2014; 173: 33-43.

[8] Rivat C, Becker C, Blugeot A, *et al*. Chronic stress induces transient spinal neuroinflammation, triggering sensory hypersensitivity and long-lasting anxiety-induced hyperalgesia. Pain 2010; 150: 358-68.

[9] Ridker PM. Inflammatory biomarkers and risks of myocardial infarction, stroke, diabetes, and total mortality: Implications for longevity. Nutr Rev 2007; 65: S253-9.

[10] Gold SM, Irwin MR. Depression and immunity: inflammation and depressive symptoms in multiple sclerosis. Neurol Clin 2006; 24: 507-19.

[11] Zautra AJ, Yocum DC, Villanueva I, *et al*. Immune activation and depression in women with rheumatoid arthritis. J Rheumatol 2004; 3: 457-63.

[12] Mossner R, Mikova O, Koutsilieri E, *et al*. Consensus paper of the WFSBP Task Force on Biological Markers: Biological markers in depression. World J Biol Psychiatry 2007; 8: 141-74.

[13] Raison CL, Capuron L, Miller AH. Cytokines sing the blues: inflammation and the pathogenesis of depression. Trends Immunol 2006; 27: 24-31.

[14] Dantzer R, O'Connor JC, Freund GG, Johnson RW, Kelley KK. From inflammation to sickness and depression: When the immune system subjugates the brain. Nat Rev Neurosci 2008; 9: 46-56.

[15] Musselman DL, Lawson DH, Gumnick JF, *et al*. Paroxetine for the prevention of depression induced by high-dose interferon alpha. N Engl J Med 2001; 344: 961-6.

[16] Schaefer M, Ertgelbrecht MA, Gut O, *et al*. Interferon alpha (IFNα) and psychiatric syndromes: a review. Prog Neuropsychopharmacol Biol Psychiatry 2002; 26: 731-46.

[17] Raison CL, Borisov AS, Broadwell SD, *et al*. Depression during pegylated interferon-alpha plus ribavirin therapy: prevalence and prediction. J Clin Psychiatry 2005; 66: 41-8.

[18] Raison CL, Borisov AS, Majer M, *et al*. Activation of central nervous system inflammatory pathways by interferon-alpha: Relationship to monoamines and depression. Biol Psychiatry 2008; 65: 296-303.

[19] Himmerich H, Fischer J, Bauer K, *et al*. Stress-induced cytokine changes in rats. Eur Cytokine Netw 2013; 24: 97-103.

[20] Chourbaji S, Urani A, Inta I, *et al*. IL-6 knockout mice exhibit resistance to stress-induced development of depression-like behaviors. Neurobiol Dis 2006; 23: 587-94.

[21] Sukoff Rizzo SJ, Neal SJ, Hughes ZA, *et al*. Evidence for sustained elevation of IL-6 in the CNS as a key contributor of depressive-like phenotypes. Transl Psychiatry 2012; 2: e199.

[22] Hamer M, Batty GD, Kivimaki M. Risk of future depression in people who are obese but metabolically healthy: the English longitudinal study of ageing. Mol Psychiatry 2012; 17: 940-5.

[23] Godha D, Shi L, Mavronicolas H. Association between tendency towards depression and severity of rheumatoid arthritis from a national representative sample: the Medical Expenditure Panel Survey. Curr Med Res Opin 2010; 26: 1685-90.

[24] Hellmann-Regen J, Piber D, Hinkelmann K, *et al*. Depressive syndromes in neurological disorders. Eur Arch Psychiatry Clin Neurosci 2013; 263(Suppl 2): S123-36.

[25] Daulatzai MA. Chronic functional bowel syndrome enhances gut-brain axis dysfunction, neuroinflammation, cognitive impairment, and vulnerability to dementia. Neurochem Res 2014; 39: 624-44.

[26] Beutler B, Hoebe K, Du X, Ulevitch RJ. How we detect microbes and respond to them: the Toll-like receptors and their transducers. J Leukoc Biol 2003; 74: 479-85.

[27] Rummel C, Inoue W, Sachot C, *et al*. Selective contribution of interleukin-6 and leptin to brain inflammatory signals induced by systemic LPS injection in mice. J Comp Neurol 2008; 511: 373-95.

[28] Lin YL, Wang S. Prenatal lipopolysaccharide exposure increases depression-like behaviors and reduces hippocampal neurogenesis in adult rats. Behav Brain Res 2014; 259: 24-34.

[29] Ji WW, Wang SY, Ma ZQ. Effects of perillaldehyde on alternations in serum cytokines and depressive-like behavior in mice after lipopolysaccharide administration. Pharmacol Biochem Behav 2014; 116: 1-8.

[30] Konsman JP, Luheshi GN, Bluthe RM, Dantzer R. The vagus nerve mediates behavioural depression, but not fever, in response to peripheral immune signals; a functional anatomical analysis. Eur J Neurosci 2000; 12: 4434-46.

[31] Ching S, Zhang H, Belevych N, *et al*. Endothelial-specific knockdown of interleukin-1 (IL-1) type 1 receptor differentially alters CNS responses to IL-1 depending on its route of administration. J Neurosci 2007; 27: 10476-86.

[32] McCusker RH, Kelley KW. Immune–neural connections: how the immune system's response to infectious agents influences behaviour. J Exp Biol 2013; 216: 84-98.

[33] Barrientos RM, Higgins EA, *et al*. Peripheral infection and aging interact to impair hippocampal memory consolidation. Neurobiol Aging 2006; 27: 723-32.

[34] Chen J, Buchanan JB, Sparkman NL, *et al*. Neuroinflammation and disruption in working memory in aged mice after acute stimulation of the peripheral innate immune system. Brain Behav Immun 2008; 22: 301-11.

[35] Müller N. Immunology of major depression. Neuroimmuno-modulation 2014; 21: 123-30.

[36] André C, Dinel AL, Ferreira G1, Layé S, Castanon N. Diet-induced obesity progressively alters cognition, anxiety-like behavior and lipopolysaccharide-induced depressive-like behavior: Focus on brain indoleamine 2,3-dioxygenase activation. Brain Behav Immun 2014; 41: 10-21.

[37] Dobos N, de Vries EF, Kema IP, *et al*. The role of indoleamine 2,3-dioxygenase in a mouse model of neuroinflammation-induced depression. J Alzheimers Dis 2012; 28: 905-15.

[38] Shelton RC, Miller AH. Eating ourselves to death (and despair): the contribution of adiposity and inflammation to depression. Prog Neurobiol 2010; 91: 275-99.

[39] Sullivan-Singh SJ, Sawyer K, Ehde DM, *et al*. Comorbidity of pain and depression among persons with traumatic brain injury. Arch Phys Med Rehabil 2014; 95(6): 1100-5.

[40] Fenn AM, Gensel JC, Huang Y, *et al*. Immune activation promotes depression 1 month after diffuse brain injury: a role for primed microglia. Biol Psychiatry 2014; 76(7): 575-84.

[41] Frick LR, Williams K, Pittenger C. Microglial dysregulation in psychiatric disease. Clin Dev Immunol 2013; 2013: 608654.

[42] Aguliar-Valles A, Kim J, Jung S, Woodside B, Luheshi GN. Role of brain transmigrating neutrophils in depression-like behavior during systemic infection. Mol Psychiatry 2014; 19: 599-606.

[43] Chen CC, Grimbaldeston MA, Tsai M, Weissman IL, Galli SJ. Identification of mast cell progenitors in adult mice. Proc Natl Acad Sci USA 2005; 102: 11408-13.

[44] Gilfillan AM, Austin SJ, Metcalfe DD. Mast cell biology: introduction and overview. Adv Exp Med Biol 2011; 716: 2-12.

[45] Lambracht-Hall M, Dimitriadou V, Theoharides TC. Migration of mast cells in the developing rat brain. Dev Brain Res 1990; 56: 151-9.

[46] Silverman AJ, Sutherland AK, Wilhelm M, Silver R. Mast cells migrate from blood to brain. J Neurosci 2000; 20: 401-8.

[47] Johnson D, Krenger W. Interactions of mast cells with the nervous system – recent advances. Neurochem Res 1992; 17: 939-51.

[48] Gauchat JF, Henchoz S, Mazzei G, *et al*. Induction of human IgE synthesis in B cells by mast cells and basophils. Nature 1993; 365: 340-3.

[49] Wardlaw AJ, Moqbel R, Cromwell O, Kay AB. Platelet-activating factor. A potent chemotactic and chemokinetic factor for human eosinophils. J Clin Invest 1986; 78: 1701-6.

[50] Perry VH, Andersson PB, Gordon G. Macrophages and inflammation in the central nervous system. Trends Neurosci 1993; 16: 268-73.

[51] Brenner T, Soffer D, Shalit M, Levi-Schaffer F. Mast cells in experimental allergic encephalomyelitis: characterization, distribution in the CNS and *in vitro* activation by myelin basic protein and neuropeptides. J Neurol Sci 1994; 122: 210-3.

[52] Theoharides TC, Baloyannis SJ, Manolidis LS. Activated rat peritoneal mast cells can cause syngeneic brain demyelination *in vitro*. Int J Immunopathol Pharmacol 1991; 4: 137-44.

[53] Medic N, Lorenzon P, Vita F, Trevisan E, *et al*. Mast cell adhesion induces cytoskeletal modifications and programmed cell death in oligodendrocytes. J Neuroimmunol 2010; 218: 57-66.

[54] Nautiyal KM, Ribeiro AC, Pfaff DW, Silver R. Brain mast cells link the immune system to anxiety-like behavior. Proc Natl Acad Sci USA 2008; 105: 18053-7.

[55] Valent P, Horny HP, Escribano L, *et al*. Diagnostic criteria and classification of mastocytosis: a consensus proposal. Leuk Res 2001; 25: 603-25.

[56] Hermine O, Lortholary O, Leventhal PS, *et al*. Case-control cohort study of patients' perceptions of disability in mastocytosis. PLoS One 2008; 3: 5.

[57] Rogers MP, Bloomingdale K, Murawski BJ, *et al*. Mixed organic brain syndrome as a manifestation of systemic mastocytosis. Psychosom Med 1986; m48: 437-47.

[58] Brintzenhofe-Szoc KM, Levin TT, Li Y, Kissane DW, Zabora JR. Mixed anxiety/depression symptoms in a large cancer cohort: prevalence by cancer type. Psychosomatics 2009; 50: 383-91.

[59] Dubreuil P, Letard S, Ciufolini M, *et al*. Masitinib (AB1010), a potent and selective tyrosine kinase inhibitor targeting KIT. PLoS One 2009; 4: 9.

[60] Paul C, Sans B, Suarez F, *et al*. Masitinib for the treatment of systemic and cutaneous mastocytosis with handicap: a phase 2a study. Am J Hematol 2010; 85: 921-5.

[61] Moura DS, Sultan S, Georgin-Lavialle S, *et al*. Depression in patients with mastocytosis: prevalence, features and effects of masitinib therapy. PLoS One 2011; 6: 10.

[62] Schaie KW. Intellectual Development in Adulthood: The Seattle Longitudinal Study. Cambridge: Cambridge University Press; 1996.

[63] Dumitriu D, Hao J, Hara Y, *et al*. Selective changes in thin spine density and morphology in monkey prefrontal cortex correlate with aging-related cognitive impairment. J Neurosci 2010; 30: 7507-15.

[64] Gómez-Isla T, Price JL, McKeel DW Jr, *et al*. Profound loss of layer II entorhinal cortex neurons occurs in very mild Alzheimer's disease. J Neurosci 1996; 16: 4491-500.

[65] Blazer D. Neurocognitive disorders in DSM-5. Am J Psychiatry 2013; 170: 585-7.

[66] Buchanan JB, Sparkman NL, Chen J, Johnson RW. Cognitive and neuroinflammatory consequences of mild repeated stress are exacerbated in aged mice. Psychoneuroendocrinology 2008; 33: 755-65.

[67] Hein AM, Stasko MR, Matousek SB, *et al*. Sustained hippocampal IL-1β overexpression impairs contextual and spatial memory in transgenic mice. Brain Behav Immun 2010; 24: 243-53.

[68] Sloane JA, Hollander W, Moss MB, Rosene DL, Abraham CR. Increased microglial activation and protein nitration in white matter of the aging monkey. Neurobiol Aging 1999; 20: 395-405.

[69] Peters O, Schipke CG, Philipps A, *et al*. Astrocyte function is modified by Alzheimer's disease-like pathology in aged mice. J Alzheimers Dis 2009; 18: 177-89.

[70] Wilson CJ, Finch CE, Cohen HJ. Cytokines and cognition--the case for a head-to-toe inflammatory paradigm. J Am Geriatr Soc 2002; 50: 2041-56.

[71] Godbout JP, Chen J, Abraham J, *et al*. Exaggerated neuroinflammation and sickness behavior in aged mice following activation of the peripheral innate immune system. FASEB J 2005; 19: 1329-31.

[72] Counts SE, Nadeem M, Lad SP, Wuu J, Mufson EJ. Differential expression of synaptic proteins in the frontal and temporal cortex of elderly subjects with mild cognitive impairment. J Neuropathol Exp Neurol 2006; 65: 592-601.

[73] Kojima N, Shirao T. Synaptic dysfunction and disruption of postsynaptic drebrin-actin complex: a study of neurological disorders accompanied by cognitive deficits. Neurosci Res 2007; 58: 1-5.

[74] Paolicelli RC, Bolasco G, Pagani F, *et al*. Synaptic pruning by microglia is necessary for normal brain development. Science 2011; 333: 1456-8.

[75] Schafer DP1, Lehrman EK, Stevens B. The "quad-partite" synapse: microglia-synapse interactions in the developing and mature CNS. Glia 2013; 61: 24-36.

[76] Stevens B, Allen NJ, Vazquez LE, *et al*. The classical complement cascade mediates CNS synapse elimination. Cell 2007; 131: 1164-78.

[77] Schafer DP, Lehrman EK, Kautzman AG, *et al*. Microglia sculpt postnatal neural circuits in an activity and complement-dependent manner. Neuron 2012; 74: 691-705.

[78] Zlokovic BV. Neurovascular pathways to neurodegeneration in Alzheimer's disease and other disorders. Nat Rev Neurosci 2011; 12: 723-38.

[79] Nizet V, Johnson RS. Interdependence of hypoxic and innate immune responses. Nat Rev Immunol 2009; 9: 609-17.

[80] Zhang J, Malik A, Choi HB, *et al*. Microglial CR3 activation triggers long-term synaptic depression in the hippocampus *via* NADPH oxidase. Neuron 2014; 82: 195-207.

[81] Selkoe D1, Mandelkow E, Holtzman D. Deciphering Alzheimer disease. Cold Spring Harb Perspect Med 2012; 2: a011460.

[82] Wyss-Coray T. Inflammation in Alzheimer disease: driving force, bystander or beneficial response? Nat Med 2006; 12: 1005-15.

[83] Medeiros R, LaFerla FM. Astrocytes: conductors of the Alzheimer disease neuroinflammatory symphony. Exp Neurol 2013; 239: 133-8.

[84] Rivest S. Regulation of innate immune responses in the brain. Nat Rev Immunol 2009; 9: 429-39.

[85] Biscaro B, Lindvall O, Tesco G, Ekdahl CT, Nitsch RM. Inhibition of microglial activation protects hippocampal heurogenesis and improves cognitive deficits in a transgenic mouse model for Alzheimer's disease. Neurodegener Dis 2012; 9: 187-98.

[86] Cleary JP, Walsh DM, Hofmeister JJ, *et al*. Natural oligomers of the amyloid-beta protein specifically disrupt cognitive function. Nat Neurosci 2005; 8: 79-84.

[87] Bachstetter AD, Norris CM, Sompol P, *et al*. Early stage drug treatment that normalizes proinflammatory cytokine production attenuates synaptic dysfunction in a mouse model that exhibits age-dependent progression of Alzheimer's disease-related pathology. J Neurosci 2012; 32: 10201-10.

[88] Newman S, Stygall J, Hirani S, Shaefi S, Maze M. Postoperative cognitive dysfunction after noncardiac surgery: a systematic review. Anesthesiology 2007; 106: 572-90.

[89] Rasmussen LS. Postoperative cognitive dysfunction: incidence and prevention. Best Pract Res Anaesthesiol 2006; 20: 315-30.

[90] Krenk L, Rasmussen LS, Kehlet H. New insights into the pathophysiology of postoperative cognitive dysfunction. Acta Anaesthesiol Scand 2010; 54: 951-6.

[91] Shapira-Lichter I, Beilin B, Ofek K, *et al*. Cytokines and cholinergic signals co-modulate surgical stress-induced changes in mood and memory. Brain Behav Immun 2008; 22: 388-98.

[92] Dilger RN, Johnson RW. Aging, microglial cell priming, and the discordant central inflammatory response to signals from the peripheral immune system. J Leukoc Biol 2008; 84: 932-9.

[93] Barrientos RM, Higgins EA, Biedenkapp JC, *et al*. Peripheral infection and aging interact to impair hippocampal memory consolidation. Neurobiol Aging 2006; 27: 723-32.

[94] Warrington JP, Ashpole N, Csiszar A, *et al*. Whole brain radiation-induced vascular cognitive impairment: mechanisms and implications. J Vasc Res 2013; 50: 445-57.

[95] Jenrow KA, Brown SL, Lapanowski K, *et al*. Selective inhibition of microglia-mediated neuroinflammation mitigates radiation-induced cognitive impairment. Radiat Res 2013; 179: 549-56.

[96] Skaper SD, Giusti P, Facci L. Microglia and mast cells: two tracks on the road to neuroinflammation. FASEB J 2012; 26: 3103-17.

[97] Osipchuk Y, Cahalan M. Cell-to-cell spread of calcium signals mediated by ATP receptors in mast cells. Nature 1992; 359: 241-4.

[98] Chakraborty S, Kaushik DK, Gupta M, Basu A. Inflammasome signaling at the heart of central nervous system pathology. J Neurosci Res 2010; 88: 1615-31.

[99] Trang T, Beggs S, Wan X, Salter MW. P2X4-receptor-mediated synthesis and release of brain-derived neurotrophic factor in microglia is dependent on calcium and p38-mitogen-activated protein kinase activation. J Neurosci 2009; 29: 3518-28.

[100] Zhang H, Yang H, He S. TNF increases expression of IL-4 and PARs in mast cells. Cell Physiol Biochem 2010; 26: 327-36.
[101] Gasque P, Singhrao SK, Neal JW, Götze O, Morgan BP. Expression of the receptor for complement C5a (CD88) is up-regulated on reactive astrocytes, microglia, and endothelial cells in the inflamed human central nervous system. Am J Pathol 1997; 150: 31-41.
[102] Griffin RS, Costigan M, Brenner GJ, *et al*. Complement induction in spinal cord microglia results in anaphylatoxin C5a-mediated pain hypersensitivity. J Neurosci 2007; 27: 8699-708.
[103] Dong Y, Benveniste EN. Immune function of astrocytes. Glia 2001; 36: 180-90.
[104] Kim DY, Hong GU, Ro JY. Signal pathways in astrocytes activated by cross-talk between of astrocytes and mast cells through CD40-CD40L. J Neuroinflammation 2011; 8: 25.
[105] Wang M, Wang X, Zhao L, *et al*. Macroglia-microglia interactions *via* TSPO signaling regulates microglial activation in the mouse retina. J Neurosci 2014; 34: 3793-806.
[106] Buckley CD, Gilroy DW, Serhan CN, Stockinger B, Tak PP. The resolution of inflammation. Nat Rev Immunol 2013; 13: 59-66.
[107] Zhu C, Solorzano C, Sahar S, *et al*. Proinflammatory stimuli control N-acylphosphatidylethanolamine-specific phospholipase D expression in macrophages. Mol Pharmacol 2011; 79: 786-92.
[108] Tabas I, Glass CK. Anti-inflammatory therapy in chronic disease: challenges and opportunities. Science 2013; 339: 166-72.
[109] Pacher P, Bátkai S, Kunos G. The endocannabinoid system as an emerging target of pharmacotherapy. Pharmacol Rev 2006; 58: 389-462.
[110] Ueda N, Tsuboi K, Uyama T. Metabolism of endocannabinoids and related N-acylethanolamines: Canonical and alternative pathways. FEBS J 2013; 280: 1874-94.
[111] Leung D, Saghatelian A, Simon GM, Cravatt BF. Inactivation of N-acyl phosphatidylethanolamine phospholipase D reveals multiple mechanisms for the biosynthesis of endocannabinoids. Biochemistry 2006; 45: 4720-6.
[112] Cravatt BF, Giang DK, Mayfield SP, *et al*. Molecular characterization of an enzyme that degrades neuromodulatory fatty-acid amides. Nature 1996; 384: 83-7.
[113] Tsuboi K, Takezaki N, Ueda N. The N-acylethanolamine-hydrolyzing acid amidase (NAAA). Chem Biodivers 2007; 4: 1914-25.
[114] Skaper SD, Facci L. Mast cell-glia axis in neuroinflammation and therapeutic potential of the anandamide congener palmitoylethanolamide. Philos Trans R Soc Lond B Biol Sci 2012; 367: 3312-25.
[115] Piomelli D, Sasso O. Peripheral gating of pain signals by endogenous lipid mediators. Nat Neurosci 2014; 17: 164-74.
[116] Bisogno T, Maurelli S, Melck D, De Petrocellis L, Di Marzo V. Biosynthesis, uptake, and degradation of anandamide and palmitoylethanolamide in leukocytes. J Biol Chem 1997; 272: 3315-23.
[117] Muccioli GG, Stella N. Microglia produce and hydrolyze palmitoylethanolamide. Neuropharmacology 2008; 54: 16-22.
[118] Facci L, Dal Toso R, Romanello S, *et al*. Mast cells express a peripheral cannabinoid receptor with differential sensitivity to anandamide and palmitoylethanolamide. Proc Natl Acad Sci USA 1995; 92: 3376-80.
[119] Franklin A, Parmentier-Batteur S, Walter L, Greenberg DA, Stella N. Palmitoylethanolamide increases after focal cerebral ischemia and potentiates microglial cell motility. J Neurosci 2003; 23: 7767-75.
[120] Luongo L, Guida F, Boccella S, *et al*. Palmitoylethanolamide reduces formalin-induced neuropathic-like behaviour through spinal glial/microglial phenotypical changes in mice. CNS Neurol Disord Drug Targets 2013; 12: 45-54.
[121] Petrosino S, Palazzo E, de Novellis V, *et al*. Changes in spinal and supraspinal endocannabinoid levels in neuropathic rats. Neuropharmacology 2007; 52: 415-22.
[122] Jhaveri MD, Richardson D, Robinson I, *et al*. Inhibition of fatty acid amide hydrolase and cyclooxygenase-2 increases levels of endocannabinoid related molecules and produces analgesia *via* peroxisome proliferator-activated receptor-alpha in a model of inflammatory pain. Neuropharmacology 2008; 55: 85-93.
[123] Ghafouri N, Ghafouri B, Larsson B, *et al*. Palmitoylethanolamide and stearoylethanolamide levels in the interstitium of the trapezius muscle of women with chronic widespread pain and chronic neck-shoulder pain correlate with pain intensity and sensitivity. Pain 2013; 154: 1649-58.
[124] Skaper SD, Facci L, Giusti P. Glia and mast cells as targets for palmitoylethanolamide, an anti-inflammatory and neuroprotective lipid mediator. Mol Neurobiol 2013; 48: 340-52.
[125] Skaper SD, Facci L, Fusco M, *et al*. Palmitoylethanolamide, a naturally occurring disease-modifying agent in neuropathic pain. Inflammopharmacology 2014; 22: 79-94.
[126] Solorzano C, Zhu C, Battista N, *et al*. Selective N-acylethanolamine-hydrolyzing acid amidase inhibition reveals a key role for endogenous palmitoylethanolamide in inflammation. Proc Natl Acad Sci USA 2009; 106: 20966-71.
[127] Solorzano C, Antonietti F, Duranti A, *et al*. Synthesis and structure-activity relationships of N-(2-oxo-3-oxetanyl)amides as N-acylethanolamine-hydrolyzing acid amidase inhibitors. J Med Chem 2010; 53: 5770-81.
[128] Saturnino C, Petrosino S, Ligresti A, *et al*. Synthesis and biological evaluation of new potential inhibitors of N-acylethanolamine hydrolyzing acid amidase. Bioorg Med Chem Lett 2010; 20: 1210-3.
[129] Yamano Y, Tsuboi K, Hozaki Y, *et al*. Lipophilic amines as potent inhibitors of N-acylethanolamine-hydrolyzing acid amidase. Bioorg Med Chem 2012; 20: 3658-65.
[130] Duranti A, Tontini A, Antonietti F, *et al*. N-(2-oxo-3-oxetanyl)carbamic acid esters as N-acylethanolamine acid amidase inhibitors: synthesis and structure-activity and structure-property relationships. J Med Chem 2012; 55: 4824-36.
[131] Li Y, Yang L, Chen L, *et al*. Design and synthesis of potent N-acylethanolamine-hydrolyzing acid amidase (NAAA) inhibitor as anti-inflammatory compounds. PLoS One 2012; 7: 8.
[132] Sasso O, Moreno-Sanz G, Martucci C, *et al*. Antinociceptive effects of the N-acylethanolamine acid amidase inhibitor ARN077 in rodent pain models. Pain 2013; 154: 350-60.
[133] Ponzano S, Bertozzi F, Mengatto L, *et al*. Synthesis and structure-activity relationship (SAR) of 2-methyl-4-oxo-3-oxetanylcarbamic acid esters, a class of potent N-acylethanolamine acid amidase (NAAA) inhibitors. J Med Chem 2013; 56: 6917-34.
[134] Vitale R, Ottonello G, Petracca R, *et al*. Synthesis, structure-activity, and structure-stability relationships of 2-substituted-N-(4-oxo-3-oxetanyl) N-acylethanolamine acid amidase (NAAA) inhibitors. ChemMedChem 2014; 9: 323-36.
[135] D'Agostino G, Russo R, Avagliano C, *et al*. Palmitoylethanolamide protects against the amyloid-β25-35-induced learning and memory impairment in mice, an experimental model of Alzheimer disease. Neuropsychopharmacology 2012; 37: 1784-92.
[136] Scuderi C, Valenza M, Stecca C, *et al*. Palmitoylethanolamide exerts neuroprotective effects in mixed neuroglial cultures and organotypic hippocampal slices *via* peroxisome proliferator-activated receptor-α. J Neuroinflammation 2012; 9: 49.
[137] Esposito E, Impellizzeri D, Mazzon E, Paterniti I, Cuzzocrea S. Neuroprotective activities of palmitoylethanolamide in an animal model of Parkinson's disease. PLoS One 2012; 7: 8.
[138] Cervellati C, Cremonini E, Bosi C, *et al*. Systemic oxidative stress in older patients with mild cognitive impairment or late onset Alzheimer's disease. Curr Alzheimer Res 2013; 10: 365-72.
[139] Schrag M, Mueller C, Zabel M, *et al*. Oxidative stress in blood in Alzheimer's disease and mild cognitive impairment: a meta-analysis. Neurobiol Dis 2013; 59: 100-10.
[140] Salim S. Oxidative stress and psychological disorders. Curr Neuropharmacol 2014; 12: 140-7.
[141] Gutierrez-Merino C, Lopez-Sanchez C, Lagoa R, *et al*. Neuroprotective actions of flavonoids. Curr Med Chem 2011; 18(8): 1195-212.
[142] Grosso C, Valentão P, Ferreres F, Andrade PB. The use of flavonoids in central nervous system disorders. Curr Med Chem 2013; 20(37): 4694-719.
[143] Xu B, Li XX, He GR, *et al*. Luteolin promotes long-term potentiation and improves cognitive functions in chronic cerebral hypoperfused rats. Eur J Pharmacol 2010; 627: 99-105.
[144] Coleta M, Campos MG, Cotrim MD, Lima TC, Cunha AP. Assessment of luteolin (3',4',5,7-tetrahydroxyflavone) neuropharmacological activity. Behav Brain Res 2008; 189: 75-82.
[145] Crupi R, Paterniti I, Ahmad A, *et al*. Effects of palmitoylethanolamide and luteolin in an animal model of anxiety/depression. CNS Neurol Disord Drug Targets 2013; 12: 989-1001.

[146] Esposito M, Paterniti I, Cuzzocrea S, *et al*. Neuroprotection by association of palmitoylethanolamide with luteolin in experimental Alzheimer's disease models: the control of neuroinflammation. CNS Neurol Disord Drug Targets 2014; 13(9): 1530-41.

[147] Paterniti I, Impellizzeri D, Di Paola R, *et al*. A new co-ultramicronized composite including palmitoylethanolamide and luteolin to prevent neuroinflammation in spinal cord injury. J Neuroinflammation 2013; 10: 91.

[148] Bossers K, Wirz KT, Meerhoff GF, *et al*. Concerted changes in transcripts in the prefrontal cortex precede neuropathology in Alzheimer's disease. Brain 2010; 133: 3699-723.

[149] Parra-Damas A, Valero J, Chen M, *et al*. Crtc1 activates a transcriptional program deregulated at early Alzheimer's disease-related stages. J Neurosci 2014; 34: 5776-87.

[150] Kang HJ, Voleti B, Hajszan T, *et al*. Decreased expression of synapse-related genes and loss of synapses in major depressive disorder. Nat Med 2012; 18: 1413-7.

[151] Lo Verme J, Fu J, Astarita G, *et al*. The nuclear receptor peroxisome proliferator-activated receptor-alpha mediates the anti-inflammatory actions of palmitoylethanolamide. Mol Pharmacol 2005; 67: 15-9.

[152] Raso GM, Esposito E, Vitiello S, *et al*. Palmitoylethanolamide stimulation induces allopregnanolone synthesis in C6 cells and primary astrocytes: involvement of peroxisome-proliferator activated receptor-α. J Neuroendocrinol 2011; 23: 591-600.

[153] Scuderi C, Esposito G, Blasio A, *et al*. Palmitoylethanolamide counteracts reactive astrogliosis induced by β-amyloid peptide. J Cell Mol Med 2011; 15: 2664-74.

[154] Fidaleo M, Fanelli F, Ceru MP, Moreno S. Neuroprotective properties of peroxisome proliferator-activated receptor alpha (PPARα) and its lipid ligands. Curr Med Chem 2014; 21(24): 2803-21.

[155] Moura DS, Sultan S, Georgin-Lavialle S, *et al*. Evidence for cognitive impairment in mastocytosis: prevalence, features and correlations to depression. PLoS One 2012; 7: 6.

[156] Felger JC, Lotrich FE. Inflammatory cytokines in depression: neurobiological mechanisms and therapeutic implications. Neuroscience 2013; 246: 199-229.

[157] Cunningham C. Microglia and neurodegeneration: the role of systemic inflammation. Glia 2013; 61: 71-90.

[158] Nelson RB, Siman R, Iqbal MA, Potter H. Identification of a chymotrypsin-like mast cell protease in rat brain capable of generating the N-terminus of the Alzheimer amyloid beta-protein. J Neurochem 1993; 61: 567-77.

[159] Norden DM, Godbout JP. Review: microglia of the aged brain: primed to be activated and resistant to regulation. Neuropathol Appl Neurobiol 2013; 39: 19-34.

[160] Salminen A, Ojala J, Kaarniranta K, *et al*. Astrocytes in the aging brain express characteristics of senescence-associated secretory phenotype. Eur J Neurosci 2011; 34: 3-11.

[161] Harrison NA, Doeller CF, Voon V, Burgess N, Critchley HD. Peripheral inflammation acutely impairs human spatial memory *via* actions on medial temporal lobe glucose metabolism. Biol Psychiatry 2014; 76(7): 585-93.

[162] Weaver JD, Huang MH, Albert M, *et al*. Interleukin-6 and risk of cognitive decline: MacArthur studies of successful aging. Neurology 2002; 59: 371-8.

[163] Furuno T, Hagiyama M, Sekimura M, *et al*. Cell adhesion molecule 1 (CADM1) on mast cells promotes interaction with dorsal root ganglion neurites by heterophilic binding to nectin-3. J Neuroimmunol 2012; 250: 50-8.

[164] Choudhuri K, Llodrá J, Roth EW, *et al*. Polarized release of T-cell-receptor-enriched microvesicles at the immunological synapse. Nature 2014; 507: 118-23.

**Received: May 21, 2014** **Revised: July 29, 2014** **Accepted: July 30, 2014**