Is there a role for the nuclear receptor PPARγ in neuropsychiatric diseases?

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Abstract

The aetiology of psychiatric diseases such as depression or schizophrenia remains largely unknown, even though multiple theories have been proposed. Although monoamine theory is the cornerstone of available pharmacological therapies, relapses, incomplete control of symptoms or failure in treatment occur frequently. From an inflammatory/immune point of view, both entities share several common hallmarks in their pathophysiology, e.g. neuroendocrine/immune alterations, structural/functional abnormalities in particular brain areas, and cognitive deficits, suggesting a dysregulated inflammatory-related component of these diseases that better explains the myriad of symptoms presented by affected individuals. In this review we aimed to explore the role and relevance of inflammatory related lipids (prostanoids) derived from arachidonic acid metabolism by identification of new inflammatory markers and possible pharmacological/dietary modulation of these compounds, with the aim of improving some of the symptoms developed by individuals affected with psychiatric diseases (a critical review of basic and clinical studies about inflammatory-related arachidonic acid metabolism on neuropsychiatric diseases is included). As a specific candidate, one of these immunoregulatory lipids, the anti-inflammatory prostaglandin 15d-PGJ2 and its nuclear receptor peroxisome proliferator-activated nuclear receptor (PPARγ) could be used as a biological marker for psychiatric diseases. In addition, its pharmacological activation can be considered as a multi-faceted therapeutic target due to its anti-inflammatory/antioxidant/anti-excitotoxic/pro-energetic profile, reported in some inflammatory-related scenarios (neurological and stress-related diseases). PPARs are activated by a great variety of compounds, the most relevant being the currently prescribed group of anti-diabetic drugs thiazolidinediones, and some cannabinoids (both endocannabinoids, phytocannabinoids or synthetic), as possible novel therapeutical strategy.

Received 11 May 2010; Reviewed 21 June 2010; Revised 6 July 2010; Accepted 26 July 2010; First published online 27 August 2010

Key words: Depression, neuroinflammation, prostanoids, PPARγ, schizophrenia.

Psychiatric diseases

Major depression and other mood disorders

‘Mood disorders’ refers to diverse clinical entities (major depression, dysthymia, bipolar disorder, etc.) which share the development of periods of depression, mania or both and, typically, symptoms of anxiety based on DSM-IV-TR criteria (APA, 2000). Although their pathophysiology is heterogeneous, all these disorders have been associated with impaired serotonergic and noradrenergic neurotransmission and neuroendocrine abnormalities (Raison et al. 2006). Apart from the monoaminergic theories of depression, which are the cornerstone of current treatments, excessive activation of the hypothalamic–pituitary–adrenal (HPA) axis, with the resultant systemic release of glucocorticoids (GCs), has been described in individuals that experience episodes of depression, and has contributed to the generation of some of the cognitive and behavioural symptoms presented (de Kloet et al. 2005). GCs, among other ‘stress mediators’, are closely related to the immune system and the inflammatory process, regulating its innate and adaptive arms, both in central nervous system (CNS) and periphery (Sorrells et al. 2009). Classical studies have demonstrated the well
known anti-inflammatory properties of GCs and undoubtedly the use of these hormones for the treatment of inflammatory-related diseases in humans has proven to be highly effective over the years. However, despite the widely accepted anti-inflammatory properties of GCs, some authors have found apparent exceptions, especially in brain, after chronic stress exposure (García-Bueno et al. 2008; Sorrells & Sapolsky, 2007). This is the so-called glucocorticoid paradox.

**Schizophrenia and other psychoses**

Schizophrenia is the paradigm of the disorders in which individuals present three major categories of symptoms: positive (i.e. hallucinations), negative (i.e. amotivation) and cognitive (some types of memory and executive function) deficits (based on DSM-IV-TR criteria). The aetiology of schizophrenia remains largely unknown but the current hypotheses proposed are: an anomalous neurodevelopmental (neurodegenerative) origin (Lewis & Levitt, 2002), impaired dopaminergic transmission in specific limbic and cortical brain areas and glutamatergic hypofunction (Stone et al. 2007). All of these hypotheses, solely or as a whole, could play important roles in the pathophysiology of the disease. However, there are several hallmarks in the cellular pathophysiology of schizophrenia, e.g. neuronal degeneration, apoptotic cell death, oligodendrocyte dysfunction and decreased neurogenesis, that can be better explained if a neuro-inflammatory process takes place in specific brain areas (basal ganglia, prefrontal cortex, hippocampus), possibly related to a state of chronic microglial activation and brain vasculature dysfunction (Hanson & Gottesman, 2005; Monji et al. 2009).

As in the case of other psychiatric diseases, the stress response mounted by schizophrenia patients is impaired (Walker et al. 2008). In this manner, stress exposure is a crucial factor in the genesis of first psychotic episodes, and the massive release of GCs could be directly related to some of the cognitive deficits presented, at the level of working memory (dependent on the frontal, parietal, anterior and cingulate cortex and parts of the basal ganglia) and episodic memory (prefrontal cortex, hippocampus) (Altamura et al. 1999; Mizoguchi et al. 2004).

In this review, the current topic that mood disorders and other psychiatric diseases such as schizophrenia could present an immune/inflammatory component is discussed against a background of possible pharmacological modulation with classical or novel immunoregulatory compounds.

**Neuroinflammation**

Inflammation is a complex set of coordinated mechanisms governed by the interaction of multiple specific mediators (cytokines, prostaglandins, chemokines, etc.) released by different types of immune cells. In spite of the presence of the blood–brain barrier (BBB), the brain responds to peripheral inflammatory stimuli by mounting a local inflammatory response called *neuroinflammation* and generating HPA axis activation, and other acute-phase responses including lethargy, somnolence, fever and anorexia, referred to collectively as ‘sickness behaviour’, with the aim of maintaining organic homeostasis when threatened by injury or infection (Allan & Rothwell, 2003).

Several pathways have been proposed to explain how systemic inflammatory/immune signals access the brain, triggering the correct neuroinflammatory cascade. Briefly, entry at circumventricular organs, transduction by peripheral nerves connected to a set of subcortical central autonomic cell groups (nucleus tractus solitarius, parabrachial nucleus), facilitated transport across the BBB, cytokine–receptor interactions at the brain–fluid interfaces (Dantzer et al. 2008) and through paracrine effects of locally released prostaglandins in non-neuronal cells of the cerebral vasculature (i.e. perivascular and endothelial cells) have all been proposed (Schiltz & Sawchenko, 2003). Once the signal is transduced, CNS parenchymal cells such as neurons, astrocytes and microglia are able to detect and to modulate the signal received, producing the same or other inflammatory mediators.

Hallmarks of CNS inflammation include: microglial activation, astrogliosis, peripheral white cell recruitment, oedema, major histocompatibility complex (MHC) expression, systemic acute-phase response protein synthesis, complement activation, accumulation of pro-inflammatory cytokines, expression and activity of pro-inflammatory mediators as nuclear factors (mainly NF-κB), inducible nitric oxide synthase-2 (NOS-2) and cyclooxygenase-2 (COX-2), expression of adhesion molecules (N-CAM) and matrix metalloproteinases (MMP-9) in peripheral cells and also in intraparenchymal brain cells (Allan & Rothwell, 2003; García-Bueno et al. 2008).

The inflammatory process is a protective mechanism, conserved during evolution in all types of organisms. However, when it is excessive in intensity (overexpression or overactivity of its mediators) and time (inefficient resolution), it becomes harmful and can exacerbate numerous diseases. There is extensive evidence that excessive inflammation within the CNS contributes to many acute and chronic degenerative
disorders (Parkinson’s disease, Alzheimer’s disease, etc.) (Gonzalez-Scarano & Balthuch, 1999), and there is also a current perception about its role in some psychiatric diseases [i.e. depression, post-traumatic stress disorder (PTSD), schizophrenial] (Dantzer et al. 2008; Hanson & Gottesman, 2005).

**Pro-inflammatory mediators: lessons from stress models**

Stress has been classically associated with the onset and progression of psychiatric diseases and, at the experimental level, many of the animal models of neuropsychiatric disease are based on stress exposure. On the other hand, stress is closely associated with the generation of the inflammatory/immune response found in individuals affected by these diseases (Altamura et al. 1999; Raison & Miller, 2003). Similarly, studies carried out with some stress protocols show a pro-inflammatory response in the brain and periphery mainly characterized by a complex cascade of consecutive inflammatory mediators (Garcia-Bueno et al. 2008).

**Glucocorticoids**

In the brain, GCs have been identified as regulators of diverse processes such as neurogenesis, neuroinflammation, neurodegeneration, memory, learning and mechanisms of adaptation (for review see McEwen, 1998). These hormones are considered anti-inflammatory, immunosuppressive and immunomodulatory under standard conditions (Raison & Miller, 2003). However, in recent years the classic view that GCs are universally anti-inflammatory has been challenged at a variety of levels, including the CNS (Sorrells et al. 2009).

In this way, numerous studies have demonstrated that under stress conditions (high levels of GCs) a consistent accumulation of pro-inflammatory mediators occurs (Garcia-Bueno et al. 2008). In addition, some studies reported microglial proliferation (a widely used indicator of neuroinflammation) after stress exposure, mediated by a GC and N-methyl-D-aspartate (NMDA) glutamate receptor-dependent mechanism (Nair & Bonneau, 2006).

**Glutamate excitotoxicity**

One of the initial processes that take place after stress exposure is the release of excitatory amino acids (glutamate and aspartate) into the synaptic cleft, reaching excitotoxic levels in some brain areas (i.e. hippocampus, prefrontal cortex) (Moghaddam, 1993). Increased extracellular glutamate binds to its ionotropic NMDA receptor whose overactivation causes a continuous excitation of neurons, inducing further glutamate release, ATP depletion and a dramatic increase in intracellular Ca$^{2+}$ levels, which eventually leads to neuronal death. Free radicals generated in this process can damage lipid components of cell membranes in a process known as lipid peroxidation (Kim & Yoon, 1998).

**Pro-inflammatory cytokines**

Many studies show how the exposure to acute stressors increases the expression of interleukin-1β (IL-1β) in CNS (Maier et al. 1999). IL-1β contributes to some of the responses that occur during stress such as monoamine and GC release, cognitive impairments and ‘depressive-like’ behaviours (Maier & Watkins, 1998). Other pro-inflammatory cytokines, such as tumour necrosis factor-α (TNF-α) are also released. TNF-α is one of the central mediators of tissue inflammation and has been implicated in the pathogenesis of stress response (Madrigal et al. 2002), with its release dependent on glutamate. Some other cytokines, such as IL-6, also appear increased after stress exposure in the brain (LeMay et al. 1990).

**NF-κB**

The nuclear transcription factor, NF-κB, is a crucial signalling mediator that is activated by stimuli of diverse nature (bacterial or viral infections, ionizing radiations as UV, free radicals, cytokines, etc.). Once activated, it translocates to the nucleus where it recognizes specific DNA sequences in the promoter of target genes among which are those that codify for proteins involved in inflammation, excitotoxicity, hypoxia, etc.

Similarly, NF-κB activation is one of the earliest events in the stress-induced inflammatory response, regulating the transcription of many acute-phase and inflammatory proteins (Black, 2006). In fact, stressors in humans and animals induce an increase of NF-κB in the cell nucleus, as well as increases in noradrenaline and GCs (Bierhaus et al. 2003; Black, 2006). We demonstrated experimentally for the first time that stress activates NF-κB in the rat brain (Madrigal et al. 2001), and later studies showed this activation after psychological stress in human peripheral blood mononuclear cells (Bierhaus et al. 2003).

As stated previously, NF-κB induces the expression of genes responsible for the accumulation of oxidative/nitrosative and inflammatory mediators that finally contribute to reversible cell damage or, in
chronic conditions, even cell death. Two main NF-κB-dependent enzymatic sources of oxidative/nitrosative mediators after stress in the brain and periphery are NOS-2 and COX-2.

**Pro-inflammatory enzymes**

NOS-2 has been implicated in excitotoxicity phenomena in multiple cellular systems and numerous neuropathological processes (Moncada et al. 1991), due to the toxic amounts of nitric oxide (NO*, NO) and subsequent peroxynitrite anion (ONOO−) generated by its activity.

COX-2 is able to produce prostanoids (e.g. prostaglandin E2, PGE2) in toxic amounts in pathological processes with a clear inflammatory component (Seibert et al. 1995). In addition, COX-2 activity can be neurotoxic because during its enzymatic activity, reactive oxygen species (ROS) are generated, contributing to oxidative/nitrosative damage (Phillis et al. 2006).

**Anti-inflammatory mediators**

All organisms have complex homeostatic mechanisms that allow them to adapt and survive stress and disease. One of the mechanisms receiving increasing interest is the role of certain lipid mediators derived from the differential activation of COX isoforms by different physiological/pathological stimuli. This mechanism is being considered as a possible endogenous regulator of the inflammatory response in neurodegenerative conditions. One of these prostanoids is the anti-inflammatory prostaglandin 15-deoxy-prostaglandin J2 (15d-PGJ2), a structural, non-enzymatic derivative of prostaglandin D2. This prostaglandin is the proposed endogenous ligand for the gamma isoform of the peroxisome proliferator-activated nuclear receptor, PPARγ (Forman et al. 1997). PPARs constitute a subfamily included in the superfamily of nuclear hormone receptors (Houseknecht et al. 2002). They act as ligand-dependent transcription factors, binding to DNA in specific regions (PPAR response elements, PPREs) and regulate the expression of genes related to lipid and glucose metabolism, inflammatory processes and cellular differentiation (Kapadia et al. 2008). Interestingly, PPARs are expressed in the great majority of brain and immune cells (Heneka & Landreth, 2007).

PPARγ and its ligands are master regulators of cerebral physiology and potential therapeutic targets for the treatment of several pathological conditions associated with neuroinflammation within CNS. Thus, the anti-inflammatory functions of PPARγ have received much attention since its agonists exert a broad spectrum of protective effects in several animal models of neurological (Alzheimer’s disease, multiple sclerosis) and cardiovascular (reviewed in Feinstein, 2003) diseases.

Similar effects have been also described in animal models of psychiatric diseases: studies from our laboratory have shown that stress enhances the production of 15d-PGJ2 and increases the expression of PPARγ in cerebral cortex as a counterbalancing anti-inflammatory/antioxidant mechanism (García-Bueno et al. 2005a,b). We have also demonstrated that both synthetic and natural PPARγ ligands prevent inflammatory and oxidative/nitrosative consequences of stress exposure in the cerebral cortex of rats subjected to restraint stress (García-Bueno et al. 2005a,b). In addition, anti-excitotoxic (decrease in NMDA transmission and increase in glutamate uptake by astrocytes) and pro-energetic (improvement in glucose uptake and increase in ATP production) mechanisms for PPARγ agonists in the stressed brain have also been demonstrated (García-Bueno et al. 2007).

All these findings suggest that the PPAR pathway may act as a mediator of ‘central neurogenic neuroprotection’, conferring protection under neuroinflammatory conditions (Galea et al. 2003) or ‘adaptive plasticity’, as proposed by McEwen (1998).

**Depression and schizophrenia as inflammatory-related CNS pathologies**

**Depression**

Increasing evidence demonstrates the importance of neuroendocrine and immune responses in the pathophysiology of depression (Maes, 1999). GC receptor dysfunction has been repeatedly reported in depression and in other disorders with affective dysregulation, suggesting a role for stress-response regulatory mechanisms (Fase et al. 2007). Abnormal GC function might be associated with inflammatory and cytotoxic processes involved in the emotional and behavioral symptoms of multiple CNS disorders (McEwen, 1998).

Patients with major depression who are otherwise medically healthy have activated inflammatory pathways, as manifested by increased pro-inflammatory cytokines, increased acute-phase proteins and increased expression of chemokines and adhesion molecules (Raison et al. 2006). In addition to effects on neurotransmitter metabolism, inflammatory cytokines have profound stimulatory effects on HPA axis hormones, including the status of hypercortisolism and
GC resistance (Wolkowitz et al. 2001). Downstream cytokine signal transduction pathways, including mitogen-activated protein kinases (MAPks) and NF-κB, also disrupt GC receptor signalling, and thus possibly contribute to altered GC-mediated feedback regulation of both corticotrophin-releasing hormone (CRH) and further pro-inflammatory cytokine release. The search for potential new therapeutic targets in depression and other related diseases through the regulation of this inflammatory pathway have recently indicated neural inputs in control of this potentially deadly cytokine response (Tracey et al. 2001). Stress-related inflammatory response could be stimulated by activation of the sympathetic adrenergic systems which in turn can stimulate the production of inflammatory factors such as NF-κB (Miller et al. 2009). On the contrary, stress-related factors can also deactivate the inflammatory response through activation of cholinergic mechanisms via stimulation of nicotinic receptors (Pavlov & Tracey, 2005). A still unexplored possibility in depressed patients is regulation by the so-called cholinergic anti-inflammatory pathway. In short, vagal withdrawal might promote inflammation, given the evidence that vagal activity inhibits NF-κB activation (and the release of TNF-α from macrophages) via cholinergic signalling. The best characterized of these cholinergic receptors that suppress cytokines is the α7 subunit of the nicotinic AChR (α7nAChR) (De Rosa et al. 2009).

The inflammatory theory of depression is also supported by some pharmacological evidence derived from the study of the possible mechanisms of action of different families of antidepressant. This study has revealed that some of these drugs possess the ability to ameliorate cytokine-induced depression, inhibiting the synthesis and/or release of pro-inflammatory cytokines and stimulating the expression of anti-inflammatory cytokines, both in animals and humans (Miller et al. 2009).

The past 10–15 years in the field of inflammation and psychiatric disease has fundamentally focused on the characterization of cytokines and GCs in the aetiology and pathophysiology of these diseases; however, the inflammatory process is constituted for a wide variety of mediators whose precise role is unknown. Some of these mediators are lipid molecules derived from the metabolism of the polyunsaturated fatty acid arachidonic acid (AA). All these compounds are generated via a complex multi-enzymatic pathway: AA, formed from membrane phospholipids by the action of phospholipase A2, is the main substrate for cyclooxygenases (COXs), which catalyse the rate-limiting conversion of AA to prostaglandin H2 (PGH2). Tissue-specific prostaglandin synthases convert PGH2 into different prostanoids, such as the prostaglandins PGE2, PGD2, PGF2, prostacyclin (PGI2) and thromboxane A2. In the case of PGE2 synthesis, microsomal PGE2 (m-PGE2) synthase-1 (m-PGES-1) is the most important and most studied E synthase-type enzyme in brain cortex (Murakami et al. 2002), and for 15d-PGJ2 synthesis, lipocalin-type PGD2 (L-PGD2) synthase (L-PGDS) is the main type (Urade & Hayaishi, 2000).

A careful meta-analysis of this complex pathway in human and animal models of the main psychiatric diseases shows the importance of a balanced lipid metabolism in their aetiology and physiopathology (Tables 1 and 2). As can be seen in Table 1, there are gene associations and a consistent increase in phospholipase activity in patients diagnosed with depression. Posterior elements of this complex pathway such as COXs are also up-regulated. A clear issue derived from several studies is the effectiveness of the use of COX-2 inhibitors (such as celecoxib) as co-adjuvant in the treatment of depression with the respective drugs currently prescribed. These findings are also demonstrated in animal models of depression (see Table 2) and the inhibitory effects of different antidepressants on COX activity and expression can be seen. In the case of the anti-inflammatory arm of this balanced prostanoid pathway, only one study (Ji-Rong et al. 2009) indicates a gene association between PPARγ and depressive individuals and more studies are needed to unequivocally link the biology of these nuclear receptors with depression. However, various studies in animal models of psychiatric diseases (Garcia-Bueno et al. 2005a,b; Kemp et al. 2009; Rosa et al. 2008) suggest a potential therapeutic use of PPAR modulation to restore neuroendocrine/immune alterations, structural/functional abnormalities in selected brain areas and cognitive and behavioural deficits. However, the antidepressant potential, although promising, needs to be fully established.

Schizophrenia

Similarly to what occurs in depression, increasing scientific evidence demonstrates a neuroinflammatory hypothesis of schizophrenia (Monji et al. 2009). Moreover, there is increasing literature based on the possible dysfunction of HPA axis in the disease (elevated baseline and challenge-induced HPA activity), and its relation with antipsychotic treatment (Walker et al. 2008). In this way, one of the effects derived from antipsychotic therapy is the fine regulation of HPA axis and the stabilization of the cognitive and
Table 1. Arachidonic acid metabolism in human psychiatric diseases

<table>
<thead>
<tr>
<th>Study</th>
<th>Psychiatric disease</th>
<th>Studied parameters</th>
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<tr>
<td>Pae et al. (2004a, b)</td>
<td>Major depressive disorder (MDD)</td>
<td>Cytosolic phospholipase A2 (cPLA2) gene polymorphism</td>
<td>BanI polymorphism is associated with ↑ risk of MDD</td>
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<tr>
<td>Peet &amp; Horrobin (2002), Puri et al. (2001), Nemets et al. (2002)</td>
<td>Depression</td>
<td>Depressive symptoms, Structural brain changes, Phospholipid turnover</td>
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<td>Eicosapentaenoic acid (EPA) improves depressive symptoms</td>
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<td>Akhondzadeh et al. (2009)</td>
<td>Major depression (MDD)</td>
<td>Symptoms of MDD</td>
<td>Fluoxetine + celecoxib reduces MDD symptoms</td>
<td>Celecoxib may be an effective adjuvant agent</td>
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<tr>
<td>Müller et al. (2006)</td>
<td>MDD</td>
<td>Hamilton Depression Rating Scale (HAMD)</td>
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<td>Celecoxib has therapeutic effects</td>
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<td>Celecoxib reduces HAMD scores</td>
<td>Celecoxib may be an effective adjuvant agent</td>
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<td>Quick Inventory of Depressive Symptoms</td>
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<td>Ji-Rong et al. (2009)</td>
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<td>Nadalin et al. (2008)</td>
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<td>BanI polymorphism is not associated with schizophrenia</td>
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<td>BanI genotype is associated with an ↑PLA2 activity</td>
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<td>Li et al. (2007), Tao et al. (2005a, b)</td>
<td>Schizophrenia</td>
<td>PL2G4A gene</td>
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<td>Yu et al. (2005), Tao et al. (2005a, b), Chowdari et al. (2001)</td>
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<td>Smesny et al. (2005), Junqueira et al. (2004)</td>
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<td>Study</td>
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<td>Gattaz et al. (1987)</td>
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<td>Plasma PLA₂ activity</td>
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<td>Schizophrenia deterioration</td>
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<td>Akhondzadeh et al. (2007)</td>
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<td>Wei &amp; Hemmings (2004)</td>
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<td>Genetic association between the PTGS2/PLA2G4A locus and schizophrenia</td>
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<td>No genetic association between the PTGS2/PLA2G4A locus and schizophrenia</td>
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<td>Sun et al. (2008)</td>
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<td>PPARα gene</td>
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<td>Bipolar disorder</td>
<td>cPLA₂-IVA, sPLA₂-IIA, COX-2 and cytosolic (cPGES) and membrane prostaglandin E synthases (mPGES) mRNAs</td>
<td>cPLA₂-IVA, sPLA₂-IIA, COX-2 and mPGES mRNAs are increased – COX1 and cPGES are reduced</td>
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<td>Cytosolic prostaglandin E2 synthase (cPGES) in cortical regions</td>
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<td>Study</td>
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<td>Song et al. (2009a, b)</td>
<td>Olfactory bulbectomy</td>
<td>Brain phospholipase A&lt;sub&gt;2&lt;/sub&gt; (PLA&lt;sub&gt;2&lt;/sub&gt;) expression</td>
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<td>Dwivedi et al. (2005)</td>
<td>Stress induced learned helplessness</td>
<td>Brain phospholipase C (PLC) activity and expression</td>
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<td>Lee et al. (2008)</td>
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<td>–</td>
<td>Cytosolic phospholipase A(2) (cPLA&lt;sub&gt;2&lt;/sub&gt;) expression</td>
<td></td>
<td>Chronic fluoxetine ↑ activity, protein and ARNm levels of cPLA&lt;sub&gt;2&lt;/sub&gt;</td>
</tr>
<tr>
<td>Rao et al. (2006), Lee et al. (2007)</td>
<td>–</td>
<td>cPLA&lt;sub&gt;2&lt;/sub&gt; activity, expression and mRNA levels</td>
<td></td>
<td>Antidepressants ↑PLC γ1</td>
</tr>
<tr>
<td>Rantamäki et al. (2007)</td>
<td>–</td>
<td>TrkB-mediated activation of PLCγ1</td>
<td></td>
<td>Fluoxetine ↑ PLA(2) signal in vivo</td>
</tr>
<tr>
<td>Qu et al. (2006)</td>
<td>–</td>
<td>PLA(2)-mediated signal transduction</td>
<td></td>
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<tr>
<td>Myers et al. (2001)</td>
<td>–</td>
<td>PLA(2) signalling: [³H]AA incorporation</td>
<td></td>
<td>Haloperidol ↓ PL2 signalling</td>
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<tr>
<td>Basselin et al. (2005a, b, 2006)</td>
<td>–</td>
<td>PLA(2) activation</td>
<td></td>
<td>Lithium chloride↑ PL2 signalling</td>
</tr>
<tr>
<td>Bosetti et al. (2002)</td>
<td>–</td>
<td>Ca&lt;sup&gt;2+&lt;/sup&gt;-independent iPLA(2) expression</td>
<td>Lithium ↓ COX-2 expression</td>
<td>No affected by lithium chloride</td>
</tr>
<tr>
<td>Song et al. (2009a, b)</td>
<td>Olfactory bulbectomy</td>
<td>Prostaglandin E&lt;sub&gt;2&lt;/sub&gt; (PGE&lt;sub&gt;2&lt;/sub&gt;) levels</td>
<td>↑PGE&lt;sub&gt;2&lt;/sub&gt;</td>
<td>EPA normalizes PGE&lt;sub&gt;2&lt;/sub&gt; levels</td>
</tr>
<tr>
<td>Guo et al. (2009)</td>
<td>Chronic unpredictable stress</td>
<td>Depressive-like behavior</td>
<td>↑Depressive-like behaviour</td>
<td>Celecoxib reverses depressive-like behavior</td>
</tr>
<tr>
<td>Myint et al. (2007)</td>
<td>Olfactory bulbectomy</td>
<td>Behavioural and immune changes</td>
<td>↑Depressive-symptoms</td>
<td>Celecoxib reverses depressive symptoms</td>
</tr>
<tr>
<td>Mizuno et al. (2007)</td>
<td>Strial administration of epidermal growth factor</td>
<td>Prepulse inhibition (PPI) and latent learning</td>
<td>↓ PPI and latent learning</td>
<td>Celecoxib ameliorates behavioural impairments</td>
</tr>
<tr>
<td>Lee et al. (2008)</td>
<td>–</td>
<td>COX-2 mRNA and protein</td>
<td>Lamotrigine ↓ COX-2 mRNA and protein</td>
<td></td>
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<tr>
<td>Rao et al. (2007a, b)</td>
<td>–</td>
<td>COX-2 mRNA</td>
<td>Sodium valproate ↓ COX-2 mRNA</td>
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<tr>
<td>Ghelardoni et al. (2005)</td>
<td>–</td>
<td>Brain protein levels of COX-1 and COX-2</td>
<td>Topiramate does not alter COX expression</td>
<td></td>
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<tr>
<td>Ghelardoni et al. (2004)</td>
<td>–</td>
<td>COX activity</td>
<td>Carbamazepine ↓COX activity</td>
<td></td>
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<tr>
<td>Bosetti et al. (2002)</td>
<td>–</td>
<td>COX-2 activity and PGE&lt;sub&gt;2&lt;/sub&gt; concentration</td>
<td>↑Immortality time</td>
<td>Lithium ↓ COX-2 activity and PGE&lt;sub&gt;2&lt;/sub&gt; concentration</td>
</tr>
<tr>
<td>Rosa et al. (2008)</td>
<td>Forced swim test</td>
<td>Immobility time</td>
<td>TZD: NP031115 antidepressant-like effect</td>
<td>Valproic acid decreases PPARy signalling</td>
</tr>
<tr>
<td>Lan et al. (2008)</td>
<td>–</td>
<td>Nuclear expression/DNA binding of PPAR</td>
<td>TZD:</td>
<td></td>
</tr>
<tr>
<td>García-Bueno et al. (2005a)</td>
<td>Restraint stress</td>
<td>Oxidative and nitrosative damage</td>
<td>↑ brain COX-2 And 15d-PGJ2</td>
<td></td>
</tr>
</tbody>
</table>

TZD, Thiazolidinediones.
–, Indicate studies in animals not subjected to previous manipulations.
behavioural symptoms resulting from its activation (cognitive deficits, social isolation, anhedonia, etc.) (Altamura et al. 1999; Walker et al. 2008).

Conversely to what occurs in stress, the glutamatergic theory of schizophrenia is based on hypothetical abnormal glutamatergic neurotransmission: in particular, glutamate NMDA receptor hypofunction has been associated with a net increase of glutamate release in some cortical areas, leading to potential excitotoxicity (Stone et al. 2007). Due to the complexity of glutamatergic neuroanatomical pathways, more studies are needed to elucidate the precise role of glutamate modulating dopamine and GABA neurotransmission and, to some extent, the positive and negative symptoms characteristic of schizophrenia patients.

Original positron emission tomography (PET) studies have contributed to the inflammatory theory of schizophrenia and other psychoses, showing microglial activation in the grey matter of schizophrenia patients during the time-frame of psychotic episodes (Doorduyn et al. 2009; van Berckel et al. 2008). In addition, there are higher microglial cell numbers in patients with psychiatric illnesses and in the post-mortem brain of psychotic patients that died from suicide (Bayer et al. 1999; Steiner et al. 2008). Similarly, other neuroimaging studies clearly associate schizophrenia with grey- and white-matter abnormalities, loss of axonal connectivity and atrophy (Bagary et al. 2003; Price et al. 2007); and several authors have proposed a direct link between chronic microglial activation (as an index on inflammation in CNS) and the pathophysiology of schizophrenia. In particular, compounds released by activated microglia as pro-inflammatory cytokines (TNF-α, IL-1β or IL-6) or free radicals and related molecules (NO, peroxinitrite anion, PGE2) produce, in other neuroinflammatory situations, some of the hallmark found in the schizophrenic brain, e.g. neuronal and oligodendrocyte degeneration, loss of glial cell numbers by apoptosis, reduced neural and vascular trophic factor synthesis, and impaired neurogenesis.

Cytokines are typically divided in Th1 (IL-2, IFN-γ) or Th2 (IL-4, IL-6, IL-10) depending on the type of T-helper cell responsible of their secretion. Th1 cells drive the type-1 pathway (‘cellular immunity’) to fight viruses and other intracellular pathogens. Th2 cells drive the type-2 pathway (‘humoral immunity’) and up-regulate antibody production to fight extracellular organisms. Schizophrenia has been associated with an imbalance in inflammatory cytokines, leading to a decrease in Th1 and an increase in Th2 cytokine secretion (Müller & Schwarz, 2008), although a systematic quantitative review has established the evidence of a different inflammatory balance in schizophrenia, challenging the current hypothesis of a Th2 decrease (Potvin et al. 2008).

Neuropsychopharmacology data demonstrated that atypical (clozapine, olanzapine, risperidone) and typical (haloperidol) antipsychotics modulate the production of pro-inflammatory cytokines (TNF-α, IL-6, IL-4, IFN-γ) (Kato et al. 2007; Leykin et al. 1997; Maes et al. 1994) and/or cytokine receptors (IL-1RA, soluble IL-2, IL-6 receptors) (Müller et al. 1997; Song et al. 2000), and their normalization correlates with improvement of psychotic symptoms (Monji et al. 2009). The increase of anti-inflammatory cytokines like IL-10 has also been demonstrated after antipsychotic treatment (Sugino et al. 2009). In addition, schizophrenia patients showed activation of NF-κB, which may play a pivotal role in the disease through interaction with pro-inflammatory cytokines (Song et al. 2009a, b).

From the clinical arena (see Table 1) is emerging the possible use of classical anti-inflammatory drugs in schizophrenia as a future therapeutic strategy. This is the case of selective COX-2 inhibitors, e.g. celecoxib, that in some prospective, randomized, double-blind studies showed therapeutic effects, improving some cognitive deficits derived form schizophrenia (Akhondzadeh et al. 2007; Müller et al. 2006). Stressing the importance of COX-related pathways in the pathophysiology of psychotic disease, increased COX-2 activation (Das & Khan, 1998) and resulting PGE2 levels (Kaiya et al. 1989) were found in schizophrenia. Recently, increased PGE4 is described as an index of CNS inflammation and it is related to glutamate transmission and metabolism, cytokines synthesis and release, acute-phase responses as HPA axis activation, fever and ‘sickness behaviour’ (Pecchi et al. 2009). As in the case of depression and bipolar mania, an increased phospholipase activity and expression has been reported in schizophrenia patients in several studies (see Table 1). Regarding the role of the anti-inflammatory arm of this pathway in schizophrenia patients, some genetic studies have reported a possible association (see Table 1), although this association is still weak and more studies, both in humans and animal models, are needed.

The other main NF-κB-dependent pro-inflammatory enzyme, NOS-2, has not yet been clearly linked to schizophrenia. However, a different isoenzyme, neuronal NOS (NOS-1), has been associated with cognitive deficits (Donohoe et al. 2009) and a NOS-1 haplotype has been associated with schizophrenia, modifying prefrontal cortex function (Reif et al. 2006). In addition, elevated and cytotoxic NO radicals have
been found in the schizophrenic brain (Yao et al. 2004) and some antipsychotics (e.g. risperidone, spiperone) inhibit NO synthesis by microglia in vitro (Kato et al. 2007).

**PPARγ as a possible therapeutic target in psychiatric disease**

Taking into account the possible common inflammatory basis of depression and schizophrenia, and the studies proposing the possibility of a chronic dysregulated inflammatory/anti-inflammatory balance in these diseases, the 15d-PGJ_2/PPARγ pathway is especially attractive due to its multiple pharmacological manipulations (García-Bueno et al. 2008).

The anti-inflammatory pathway 15d-PGJ_2/PPARγ as biological marker for psychiatric disease

The continued search for biological markers that can be objectively quantified with a high degree of accuracy is particularly useful for the difficult diagnosis of psychiatric diseases. This is one of the key areas of current psychiatric research.

The anti-inflammatory pathway 15d-PGJ_2/PPARγ could be used as a biological marker in psychiatric diseases because it is drastically modulated in both brain and/or peripheral immune cells in response to acute pro-inflammatory/oxidative stimuli or in chronic pro-inflammatory conditions, which might be the case in the brain and plasma of individuals with psychiatric disease in some particular states of the disease, such as first psychotic or depressive episodes. Several studies, using the administration of lipopolysaccharide (LPS) to elicit ‘depressive-like behaviour’ (severe sepsis or sustained infusion of LPS to rats), have demonstrated down-regulation of PPARs in liver and other peripheral tissue (Zhou et al. 2008). As stated previously, clinical data (see Table 1) relates a polymorphism in the PPARγ_2 gene (1Pro12Ala) in depression (Ji-Rong et al. 2009) and the PPARγ_1/δ gene in schizophrenia and bipolar disorder, particularly in human populations (Sun et al. 2008; Zandi et al. 2008). The analysis of 15d-PGJ_2/PPARγ in unaffected family members of patients could determine whether alterations to these anti-inflammatory molecules is a consequence of disease stage or an aetiological factor that intervenes in the disorder.

**PPARγ activation as a multi-faceted therapeutical target in psychiatric disease**

As seen previously, synthetic and natural PPARγ ligands prevent the inflammatory and oxidative/nitrosative consequences of exposure to stress in the CNS (García-Bueno et al. 2005a, b). PPARγ agonists are able to reduce the expression of pro-inflammatory mediators released by activated microglia whose activation contributes to the inflammatory damage observed in certain neurological and psychiatric diseases (Dantzer et al. 2008; Gonzalez-Scarano & Baltuch, 1999). In addition, PPARγ agonists may also activate antioxidant pathways such as nuclear factor (erythroid-derived 2)-like 2 (Nrf2) and glutathione (Park et al. 2004).

Other possible neuroprotective mechanisms afforded by treatment with PPARγ agonists are derived from studies carried out on restraint-stress paradigms. In this manner, treatment with PPARγ agonists exerts direct protective action on the cerebral glucose and glutamate metabolism disrupted after stress exposure (increasing the expression and activity of the neuronal glucose transporter GLUT-3 and the predominant glial glutamate transporter EAAT-2), mechanisms to add to its above-discussed anti-inflammatory/antioxidant effects, adding new therapeutic implications to the management of patients at risk of stress-related diseases, e.g. depression or schizophrenia (García-Bueno et al. 2007).

Elucidation of the beneficial effects of PPAR activation in glutamate metabolism, neurotransmission and excitotoxicity, which are deeply disrupted in the brain of individuals with psychiatric disease, is an enormous and critical challenge confronting future research (McNally et al. 2008; Stone et al. 2007) that could help in the development of animals models of schizophrenia (Gaspar et al. 2009).

On the other hand, PPARs are constitutively expressed in vascular-related cells and the treatment with their agonists could regulate the abnormal cerebral blood flow and glucose metabolism reported in individuals with psychiatric disease (Buchsbaum & Hazlett, 1998; Drevets, 1998; Hanson & Gottesman, 2005). Its constitutive presence in endothelial and perivascular cells (a subset of brain-resident macrophages) suggests an important role in the regulation of infiltration of immune cells across the BBB, its permeability [regulation of expression and activity of matrix metalloproteases (Pereira et al. 2006)] and the transduction of peripheral immune signals (e.g. GCs, pro-inflammatory cytokines and prostaglandins) within the brain parenchyma to initiate a potentially deleterious neuroinflammatory process.

In addition, in a neurodevelopmental situation, the endogenous PPARγ agonist 15d-PGJ_2 plays a neuroprotective role by inducing neuronal growth factor and brain-derived neuronal factor production in
astrocytes (Toyomoto et al. 2004), an effect that could be beneficial in conditions in which these and other trophic factors are dysregulated, such as in schizophrenia and some mood disorders (Buckley et al. 2007; Martinowich et al. 2007).

Thiazolidinediones (TZDs), e.g. rosiglitazone or pioglitazone, are potent agonists of PPARγ, widely used as insulin-sensitizing drugs for the treatment of type 2 diabetes (Lehmann et al. 1995). They constitute a putative treatment for neurocognitive deficits associated with mood and psychotic syndromes, by means of a myriad of mechanisms, notably insulin signalling, anti-inflammation, GC activity and cellular metabolism (McIntyre et al. 2007). In this way, some studies have reported antidepressant-like effects of these compounds in animal models of depression such as Porsolt’s, open-field and tail-suspension tests (Eissa Ahmed et al. 2009; Rosa et al. 2008).

In a remarkable and novel mechanism rosiglitazone might improve cognition by increasing dendritic spine density in discrete brain areas (Brodbeck et al. 2008). The precise mechanism remains elusive but rosiglitazone might increase mitochondrial biogenesis or function, thereby improving synaptogenesis and memory formation (Brodbeck et al. 2008). PPARγ interactions with mitochondria are especially attractive because mitochondrial abnormalities and deficiencies in oxidative phosphorylation have been reported in individuals with schizophrenia, bipolar disorder, and major depressive disorder, correlating increased

Table 3. Current neuropsychiatric treatments and PPARγ-related neuroprotective effects

<table>
<thead>
<tr>
<th></th>
<th>Anti-inflammatory/oxidant</th>
<th>Anti-excitotoxic</th>
<th>↑Neurotrophic factors</th>
<th>Pro-neurogenesis</th>
<th>Brain glucose metabolism</th>
<th>↑Neuroplasticity</th>
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</thead>
<tbody>
<tr>
<td><strong>Antidepressants</strong></td>
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<tr>
<td>Various SSRI (Hernández et al. 2008)</td>
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<tr>
<td>Imipramine (Michael-Titus et al. 2000)</td>
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<tr>
<td>Tranylcypromine, sertraline, desipramine, mianserin (Nibuya et al. 1995)</td>
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<tr>
<td>Tranylcypromine, fluoxetine, reboxetine (Malberg et al. 2000)</td>
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<tr>
<td>Citalopram (Smith et al. 2009)</td>
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<td>Amitriptyline (Norholm &amp; Ouimet, 2001)</td>
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<td><strong>Antipsychotics</strong></td>
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<tr>
<td>Clozapine (Song et al. 2000)</td>
<td>x</td>
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<tr>
<td>Haloperidol (Sinor et al. 2000)</td>
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<td>Haloperidol, risperidone (Angelucci et al. 2000)</td>
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<td>Olanzapine (Kodama et al. 2004)</td>
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<td>Clozapine (Molina et al. 2005)</td>
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<td>Haloperidol (Konradi &amp; Heckers, 2001)</td>
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<td><strong>Mood stabilizers</strong></td>
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<tr>
<td>Valproate (Zhang et al. 2008)</td>
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<tr>
<td>Lithium, valproate (Shao et al. 2005)</td>
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<td>Lithium, valproate (Yasuda et al. 2009)</td>
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<td>Lithium (Wexler et al. 2008)</td>
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<td>Lithium (Kohno et al. 2007)</td>
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<tr>
<td>Valproate (Hall et al. 2002)</td>
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psychiatric symptoms with declines in mitochondrial functional activity (Jou et al. 2009; Rollins et al. 2009).

All this scientific evidence has motivated the development of some clinical trials regarding the use of PPARγ agonists as adjuvant strategy for the treatment of diverse psychiatric diseases [see ongoing studies NCT00671515, NCT01109030 and NCT00835120 at NIH’s webpage: Clinical Trials.gov], some of which have been already published (Rasgon et al. 2010).

Possible PPAR-related mechanisms of current treatments in psychiatric diseases

Currently, a direct effect of classical treatments for psychiatric diseases on the 15d-PGJ2/PPARγ pathway has not been reported. However, administration of some of these drugs to humans, or in animal models of disease, produces the same beneficial effects as those derived from PPARγ activation (some examples of the emerging literature can be found in Table 3), which suggests some shared mechanisms of action. As shown in Table 3, some antidepressant, antipsychotic and mood-stabilizer drugs produce antioxidant/anti-inflammatory effects in the brain and periphery, mainly at the level of cytokine release. The anti-excitotoxic effects of currently used drugs are at the level of NMDA receptor activity. In general, the effects on neurogenesis rate are associated with a restoration of brain-derived neurotrophic factor (BDNF) levels in the brain. Finally, some of these drugs modulate brain glucose metabolism in particular brain areas (as a function of the disease studied) and increase neuroplasticity affecting axonal and dendritic structure and function.

Cannabinoids as PPAR agonists, a convergent role in psychiatric disease?

All the scientific evidence presented suggests an inflammatory/immune basis for these pathologies and justifies the search for new active drugs in this pathway to be used as anti-inflammatory/immuno-modulatory compounds.

Of particular interest is the use of exogenous or endogenous cannabinoids, due to their potent anti-inflammatory/antioxidant/anti-excitotoxic profile (van der Stelt et al. 2002), and their implication in the regulation of adult neurogenesis (Galve-Roperh et al. 2007; Marchalant et al. 2009). Neurogenesis is possibly disrupted in depressed and schizophrenia patients and it can be related to some structural abnormalities and cognitive deficits that are characteristic of these.
diseases (deficits in memory, learning, executive function, etc.) (Balu & Lucki, 2009; Eisch et al. 2008). Further research is needed to elucidate the exact role of these compounds in their multi-faceted pathophysiology.

The vast majority of the central effects of cannabinoids are attributed to CB1 receptor-dependent binding, but pharmacological inhibition and studies using CB1/CB2 KO mice suggest other possible mechanisms of action. Interestingly, alternative candidates are the nuclear receptors PPARs, which have diverse cannabinoids as potent ligands (O’Sullivan, 2007).

The main endocannabinoids, anandamide and 2-arachidonoylglycerol, and also ajulemic acid, a structural analogue of the phytocannabinoid Δ9-tetrahydrocannabinol (THC), have anti-inflammatory properties mediated by PPARγ. Other cannabinoiinds which activate PPARγ include N-arachidonoyldopamine, THC, cannabidiol, HU210, WIN55212-2 and CP55940. In addition, the endogenous acylethanolamines, oleoylethanolamide and palmitoylethanolamide have neuroprotective effects mediated through PPARα (Sun & Bennett, 2007). Some current studies indicate a role for CB1 receptor and a possible antidepressant role for CB1 agonists in experimental models (S. Zoppi & J. C. Leza, personal communication).

However, caution should be exercised in the pharmacological modulation of the endocannabinoid system or in the administration of exogenous cannabinoids because there is substantial evidence that cannabis abuse during adolescence is a vulnerability factor for the development of psychosis in adulthood (Le Bec et al. 2009). In addition, the endocannabinoid system is altered in schizophrenia and dysregulation of this system can be integrated in the neurodevelopmental and neuroinflammatory hypotheses of schizophrenia (Fernandez-Espejo et al. 2009).

The promising role of PPAR ligands, including endocannabinoids and/or synthetic cannabinoids without the psychotropic effects associated with CB1 binding and its consequent recreational use, for the treatment of diverse psychopathologies with an inflammatory basis deserves further consideration and scientific effort in order to elucidate the mechanism(s) involved (Burstein et al. 2004).

Concluding remarks

A dysregulated inflammatory response could explain some of the still unknown areas derived from the current theories to explain the origin of psychiatric diseases, but further studies are needed to determine whether neuroinflammation is a cause or consequence of these diseases, whether the nature of the inflammatory response is predominantly chronic or episodic and to identify the nature and precise role of every family of inflammatory mediators in the panoply of symptoms conforming the complex physiopathology of psychiatric disease. It is possible that two of the main challenges of this field are (i) to elucidate the precise role of stress exposure in the aetiology and physiopathology of each particular psychiatric disease, taking into account that stress modulates the inflammatory/immune response, acute phase responses (fever, motor deficits), cognition, memory and behaviour (anorexia, anhedonia); and (ii) the analysis of pro-inflammatory/immune parameters in subjects in a particular ‘naive’ state of the disease, such as first psychotic or depressive (without medication) episodes, given the fact that several antidepressants and antipsychotics strongly modulate pro-inflammatory mediators (cytokines, prostanoids, etc.) and could be confounder factors.

From the inflammation side of this field much work has been done in the characterization of the role of cytokines and GCs in this association, but other inflammatory mediators derived from the metabolism of arachidonic acid seem to be an emerging target for exploration. However, although more scientific evidence is needed, nuclear receptors (PPARs) have an interesting potential as biological markers for neuropsychiatric diseases, and their pharmacological modulation can represent a promising multi-faceted (see Fig. 1) therapeutic target to consider in the future.

Acknowledgements

Financial support of Dr Leza’s laboratory was received from Spanish Ministries of Science and Innovation (SAF07-63138) and Health (CIBERSAM), University Complutense-Santander (GR88/08, UCM SAL 2878-920140) and Regional Governement of Madrid (S-SAL/0261/2006).

Statement of Interest

None.

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