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For whom the endocannabinoid tolls: modulation of innate immune function and implications for psychiatric disorders

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Abbreviations: 2-AG 2-arachidonyl glycerol; AEA anandamide; CB cannabinoid receptor; CBD cannabidiol; COX-2 cyclooxygenase 2; ERK1/2extracellular signal-regulated kinase ½; FAAH fatty acid amide hydrolase; IFN interferon; IL interleukin; iNOS inducible nitric oxide synthase; IP10 Interferon gamma-induced protein 10; IRF interferon regulatory transcription factor; LPS lipopolysaccharide; MAGL monoacylglycerol lipase; MAPK mitogen-activated protein kinase; NF-κB Nuclear factor kappa B; NO nitric oxide; PAMPs pathogen-associated molecular patterns; PBMCs peripheral blood mononuclear cells; Poly I:C Polyinosinic:polycytidylic acid; PPAR peroxisome proliferator-activated receptor; THC, Δ^9-tetrahydrocannabinol; TLR Toll-like receptors; TMEV Theiler's encephalomyelitis virus; TNF tumour necrosis factor; TRIF TIR domain-containing adaptor inducing IFN-β

Classes of cannabinoid-based pharmacological agents cited in the review

Nonselective CB_1/CB_2 agonists: Δ^9-THC, HU210, CP55940, WIN55,212-2

Selective CB_2 agonists: JWH-015

FAAH inhibitors: URB597, AA-5HT

MAGL/ABHD6 inhibitors: JZL184, MJN110, KML129, WWL70

Endocannabinoid reuptake inhibitors: UCM707, OMDM1/2, AM404

Abstract

Toll-like receptors (TLRs) mediate the innate immune response to pathogens and are critical in the host defence, homeostasis and response to injury. However, uncontrolled and aberrant TLR activation can elicit potent effects on neurotransmission and neurodegenerative cascades and has been proposed to trigger the onset of certain neurodegenerative disorders and elicit detrimental effects on the progression and outcome of established disease. Over the past decade, there has been increasing evidence demonstrating that the endocannabinoid system can elicit potent modulatory effects on inflammatory processes, with clinical and preclinical evidence demonstrating beneficial effects on disease severity and symptoms in several inflammatory conditions. This review examines the evidence supporting a modulatory effect of endocannabinoids on TLR-mediated immune responses both peripherally and centrally, and the implications for psychiatric disorders such as depression and schizophrenia.

Keywords: Endocananbinoid; Anandamide; 2-AG; TLR3; TLR4; LPS; Poly I:C; depression; schizophrenia

Introduction

The endocannabinoid system is an important lipid signalling system involved in modulation of a host of physiological responses ranging from appetite, respiration, metabolism, inflammation, pain and neurotransmission to name but a few. Of particular interest over the past decade has been the discovery that cannabinoids (plant-derived, synthetic and endogenous) elicit potent modulatory effects on inflammatory processes, with clinical and preclinical evidence demonstrating beneficial effects on disease severity and symptoms in several inflammatory conditions (Yoshihara et al., 2005, Storr et al., 2009, Tschop et al., 2009, Yu et al., 2010). However, the precise mechanisms by which cannabinoids modulate immune function depend on the conditions under investigation, and in many cases remain to be determined. There has been increasing data to suggest that one mechanism by which cannabinoids influences innate immune function may be by interacting with a superfamily of pattern recognition receptors (PRR) namely toll-like receptors (TLRs). Activation of TLRs participates in host defences, homeostasis and response to injury however, uncontrolled and aberrant TLR activation can elicit potent effects on neurotransmission and neurodegenerative cascades [for reviews see (Owens, 2009, van Noort and Bsibsi, 2009, Lehnardt, 2010, Arroyo et al., 2011)]. Furthermore, viral and bacterial induced activation of TLRs results in systemic and central inflammation, an effect proposed to trigger the onset of some neurodegenerative disorders (Deleidi and Isacson, 2012) and elicit detrimental effects on the progression and outcome of established disease (Perry, 2004, Holmes et al., 2009, Teeling and Perry, 2009). As TLRs are expressed on neurons, astrocytes and microglia within the CNS (Bsibsi et al., 2002), and TLR expression has been reported to be increased in the post-mortem brain of patients with neurodegenerative and psychiatric disorders (Salaria et al., 2007, Brudek et al., 2013), modulation of TLR-associated innate inflammatory responses by cannabinoids may provide a novel therapeutic target for such disorders.

The endocannabinoid system

The endocannabinoid system is widely expressed in all tissues of the body and comprises the cannabinoid $(CB)_1$ and CB_2 receptors, the naturally occurring endogenous receptor agonists or so-called endocannabinoids, the best characterised of which are arachidonyl ethanolamide (anandamide, AEA) and 2-arachidonoyl glycerol (2-AG) (Devane et al., 1992, Mechoulam et al., 1995, Sugiura et al., 1995), and the enzymes involved in their synthesis and degradation. It should be noted that other endocannabinoid ligands including oleamide (Leggett et al., 2004), O-arachidonoyl ethanolamine (virodamine) (Porter et al., 2002), 2-arachidonoyl glycerol ether (noladin ether) (Hanus et al., 2001) and N-arachidonoyl-dopamine (NADA) (Huang et al., 2001, Bisogno et al., 2005) have been identified however, the role of these ligands in physiological processes has not been examined in detail. Endocannabinoids are not stored in vesicles but rather their biosynthesis occurs on demand via hydrolysis of cell membrane phospholipid precursors. AEA, and two related analogues *N*-oleoylethanolamide (OEA) and N-palmitoylethanolamide (PEA), formed from the precursor *N*-arachidonoylphosphatidylethanolamine (NAPE), with AEA formed due to the hydrolytic activity of the phospholipase D enzyme NAPE-PLD (Di Marzo et al., 1994, Sugiura et al., 1996). The main biosynthetic pathway for 2-AG involves the hydrolysis of the membrane phospholipid phosphatidylinositol (PI) by phospholipase C (PLC), producing 1,2-diacylglycerol (DAG), which in turn is then converted to 2-AG by diacylglycerol lipase (DAGL) (Prescott and Majerus, 1983, Sugiura et al., 1995).

Once release, endocannabinoids elicit their effect primarily via CB_1 and/or CB_2 receptors. CB_1 receptors are G-protein coupled receptors that are highly expressed throughout the human and rodent brain, with particularly high density on the pre-synaptic terminals of GABA and glutamate neurons (Herkenham et al., 1991, Tsou et al., 1998, Mackie, 2008). Activation of CB_1 receptors results in inhibition of cyclic AMP, activation of MAPK and inhibition of N- and P/Q- type voltage-activated Ca^{2+} channels while concurrently activating the inwardly rectifying K^+ currents, effects which result

in the inhibition of central neurotransmitter release. Although at lower density than on neurons, CB_1 receptors have also been shown to be expressed on glia and on a wide range of peripheral tissues (Galiegue et al., 1995, Carlisle et al., 2002, Osei-Hyiaman et al., 2005, Cavuoto et al., 2007, Cota, 2007). In comparison, CB_2 receptors, also a G-protein coupled receptor, is widely distributed in peripheral tissues, particularly in immune tissues including the spleen, tonsils, thymus, mast cells and blood cells (Munro et al., 1993, Berdyshev, 2000, Sugiura et al., 2000) and on activated glia within the brain (Carlisle et al., 2002, Nunez et al., 2004, Rock et al., 2007). Accumulating evidence has also indicated that CB_2 receptor protein and mRNA is also expressed on subsets of neurons within the brain (Van Sickle et al., 2005, Gong et al., 2006, Onaivi et al., 2006, Baek et al., 2008, Zhang et al., 2014) and thus this receptor may also directly modulate neurotransmission. In addition to CB_1 and CB_2, endocannabinoids are now known to also elicit activity at other receptors, namely the transient receptor potential vanilloid 1 (TRPV1), PPARs, GPR55 and GPR119 (Huang et al., 2002, Overton et al., 2006, Sun et al., 2006, Ryberg et al., 2007). Activity at these receptors has been proposed to account, at least partially, for some of the differential effects observed with potent selective cannabinoid agonists and modulation of endocannabinoid tone.

A number of enzymes have been identified that are involved in the catabolism of endocannabinoids. Fatty acid amide hydrolase (FAAH) has been identified as the enzyme primarily responsible for the metabolism of AEA, exhibiting similar distribution to CB_1 receptors (Cravatt et al., 1996, 2001, Walker et al., 2002). In comparison, monoacylglycerol lipase (MAGL) is considered the primary enzyme involved in 2-AG inactivation, responsible for approximately 85% of its metabolism (Dinh et al., 2002, Long et al., 2009a). The remaining 15% is thought to be broken down by FAAH, cyclooxygenase-2 (COX2), ABDH6 (serine hydrolase α/β-hydrolase domain) and ABDH12 (Blankman et al., 2007). Moreover, both COX-2 and lipoxygenase (LOX) catalyse the oxidation of AEA and 2-AG into metabolic products which mediate biological effects independent of cannabinoid receptors (Ueda et al., 2011, Urquhart et al., 2014).

Due to the topography of this lipid signalling system, the endocannabinoid system is in a unique position to regulate a host of physiological activities. Over the past decade there has been increased interest in cannabinoid modulation of immune function in both health and disease, which has been examined in detail by several excellent reviews (Nagarkatti et al., 2009, Stella, 2009, Jean-Gilles et al., 2010, Stella, 2010, Rom and Persidsky, 2013). The general consensus is that cannabinoid modulation of inflammatory processes provides a novel therapeutic target for central and peripheral inflammatory disorders. We propose that one of the mechanisms by which cananbinoids (both exogenous and endogenous) influence immune function is via modulation of TLR-mediated responses and thus the aim of this review is to examine the evidence supporting a modulatory effect of cannabinoids on TLR-mediated immune responses both peripherally and centrally, and review the implications for psychiatric disorders such as depression and schizophrenia.

Toll-like Receptors and innate immune function

The innate immune system is critical in mediating the body's physiological response to invading pathogens and self antigens [For reviews of innate immunity and pathogen host interaction see (Basset et al., 2003, Akira et al., 2006)]. Comprised of cells including monocytes/macrophages, fibroblasts, mast cells, neutrophils, natural killer and dendritic cells, as well as other circulating leukocytes, the innate immune response is mediated and orchestrated by a diverse range of pattern recognition receptors (PRRs) located on these cells which recognise pattern associated molecular patterns (PAMPS), the molecular signatures of microbes. The most widely studied of the PRRs is a class of type-I transmembrane glycoprotein's known as Toll-like receptors (TLRs). Thirteen TLRs have been identified to date; TLRs 1-9 are conserved among humans and mice, TLR10, 12 and 13 are found in humans only while TLR11 is expressed only in mice. TLRs are divided into subgroups based on their ability to recognise particular PAMPs; TLR1-2, TLR4-6 and TLR10-12 sense

microbial membrane components while TLR3, TLR7-9 and TLR13 sense microbial and viral nucleic acids. A comprehensive review of TLR signalling is beyond the scope of this article and has been extensively covered in several excellent reviews (Akira et al., 2006, Akira, 2011, Gangloff, 2012). As such, provided here is an overview of the main classes of TLRs and their primary mechanism of action. Extracellular membrane bound TLRs include TLR4 and the associated MD-2 molecule which recognizes lipopolysaccharide (LPS) present on the cell wall of gram negative bacteria; TLR2 in conjunction with TLR1, TLR6 or TLR10 recognizes bacterial associated triacyl and diacyl portions of lipoproteins; and TLR5 and TLR11 recognizes flagellin, the major component of bacterial flagella. In comparison, the intracellular TLRs, located in the endosome, include TLR3 which recognizes double-stranded RNA released from viruses; TLR7-8 recognizes single-stranded RNA; TLR9 recognizes bacterial and viral DNA and TLR13 which recognizes bacterial ribosomal RNA. In addition, TLRs are known to be activated by several damage-associated molecular patterns (DAMPs) released form stressed cells such as heat shock proteins (e.g. HSP70) and ATP; and environmental factors such as ozone and toluene [reviewed in (Asea, 2008, Lucas and Maes, 2013, Schaefer, 2014)]. Following binding of the ligand, TLRs oligomerise and signal via various adaptor molecules such as myeloid differentiation primary response gene 88 (MyD88), Toll-interleukin 1 receptor (TIR)-domain-containing adaptor-inducing interferon-β (TRIF), TIR-domain containing adaptor protein (TIRAP) and TRIF-related adaptor molecule (TRAM). MyD88 is involved in all TLR signalling except for TLR3 which signals via the MyD88-independent pathway TRIF, resulting in the activation of the transcription factor interferon regulatory factor 3 (IRF3) and subsequent production of the type 1 interferons, IFNα and IFNβ [Figure 1]. In comparison, activation of the MyD88 pathway results in activation of several signalling cascades, the translocation of the transcription factor NFκB to the nucleus and the enhanced expression of chemokines, interferons and pro-inflammatory cytokines such as IL-1β, IL-6 and TNFα [Figure 1] [for reviews of signalling mechanisms of TLRs see (Akira and Takeda, 2004, Mogensen, 2009)]. Taken together, activation of

TLRs induces an innate inflammatory state that acts to recruit macrophages and neutrophils and phagocytose invading pathogens, limit infection and promote healing. In addition, peripheral inflammatory mediators produced in response to TLR activation can communicate with the central nervous system via several routes, including entering the brain via the circumventricular organs, transported across the blood brain barrier via transport molecules expressed on brain endothelial cells, or cytokine-induced activation of the vagal communication pathway [for review of brain-immune communication pathways see (Dantzer, 2004, Quan and Banks, 2007)]. This ultimately results in activation of microglia, the production of further chemokines and cytokines that then mediates a sickness response characterised by fever, hypolocomotion, hyperalgesia, anorexia, anhedonia and activation of the stress-hypothalamic-pituitary adrenal (HPA) axis. These symptoms are collectively considered to represent a highly organised strategy of an organism to fight infection, which acts to conserve energy, reduce bacterial/pathogen replication, stimulate proliferation of immune cells and minimize thermal loss in the host (Dantzer, 2001, 2004). In addition, microglia, astrocytes, neurons and oligodendrocytes also express multiple functional TLRs (van Noort and Bsibsi, 2009) which are important in mounting immune responses against microbial invasion of the CNS. Thus, TLR signalling is crucial for peripheral and central innate immune responses, however if not tightly controlled can contribute to and/or exacerbate various diseases and disorders [reviewed in (O'Neill et al., 2009, Kawai and Akira, 2010, Lehnardt, 2010)]. Modulation of TLR-associated inflammatory responses has therefore been highlighted as a therapeutic target for a range of disorders. To date, numerous negative regulators of TLR signalling have been identified which down regulate TLR expression, block recruitment of signalling molecules, cause degradation of target proteins and negatively regulate transcription [reviewed in (Takeda and Akira, 2007, Lucas and Maes, 2013)]. Provided herein is the evidence that the endocannabinoid system may provide a further means of modulating in TLR-associated inflammatory responses and the possible implications for psychiatric disorders.

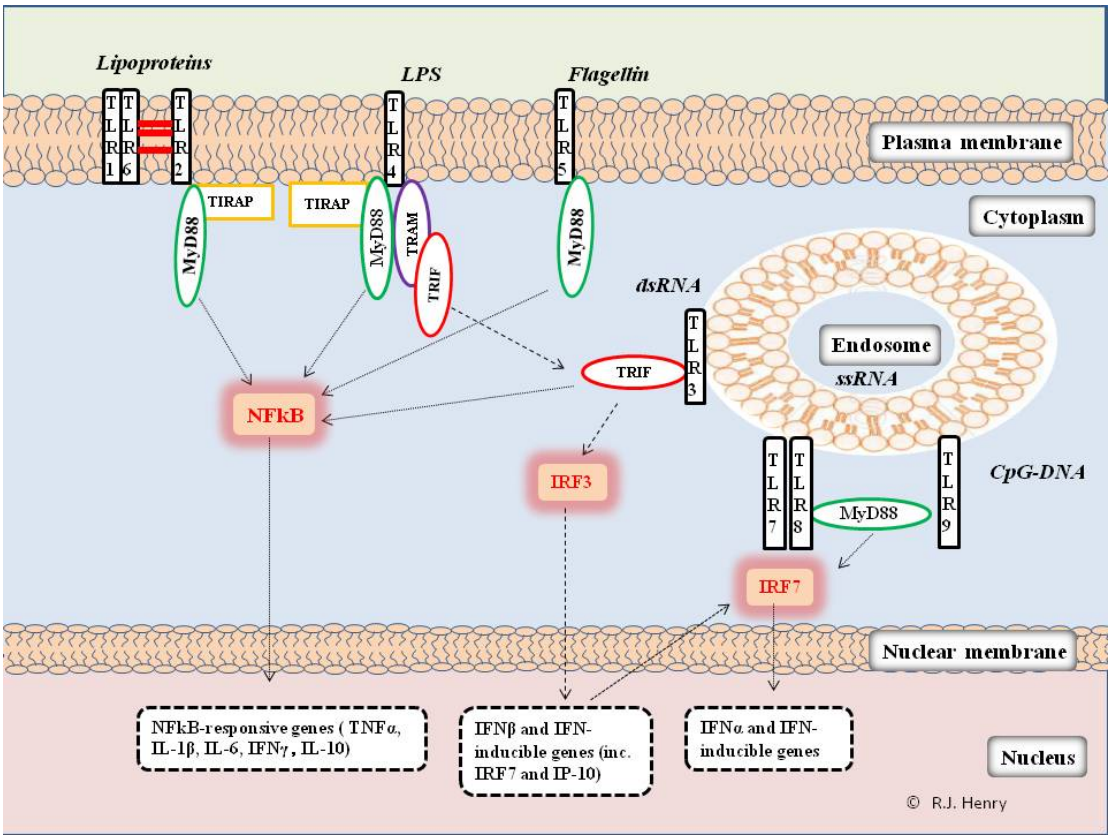

Fig 1: Primary location and signalling pathways for TLR1-9. All TLRs signal via the adaptor MyD88, except TLR3 which signals via TRIF.

Endocannabinoid modulation of TLR4-induced inflammatory responses

TLR4 is the most characterised TLR, responsible for inducing inflammatory responses to gram negative bacterial antigens. In order to activate TLR4, lipopolysaccaride (LPS), a component of the wall of gram-negative bacteria, interacts with circulating LPS binding protein (LBP) which in turn enables the association between LPS and CD14 and consequently facilitates the transfer of LPS to the TLR4/MD-2 receptor complex. Binding of LPS to TLR4, causes the receptor to dimerise and activate the MyD88 dependant pathway resulting in translocation of NFkB to the nucleus with consequent enhancement of transcription and translation of pro-inflammatory mediators such as chemokines and cytokines including IL-1β, TNF-α and IL-6, which mediate a concerted physiological response to fight infection. Due to the well recognised molecular mechanism underpinning TLR4-induced inflammatory responses, LPS is a very useful pharmacological tool with which to investigate peripheral and central immune processes and their modulation.

Some of the first evidence demonstrating a possible immunomodulatory role for the endocannabinoid system emerged from research investigating the effects of cannabinoids on TLR4-induced inflammatory responses *in vitro*. For example, potent non-selective cannabinoid receptor agonists such as Δ^9-THC, HU210, CP55940 and WIN55,212-2 have been shown to inhibit TLR4-induced pro-inflammatory cytokine and nitric oxide release, induce apoptosis and inhibit migration of macrophages (Jeon et al., 1996, Chang et al., 2001, Klegeris et al., 2003). Furthermore, these compounds have also been demonstrated to inhibit TLR4-induced inflammatory responses in microglial and astrocyte cultures (Puffenbarger et al., 2000, Facchinetti et al., 2003a), highlighting an important role in modulation of neuroinflammatory responses. Due to the high expression of CB_2 receptors on immune cells and activated glia it was not surprising that many researchers attributed the anti-inflammatory effects of cannabinoids to activity at this receptor. However, while some of these studies demonstrated that modulation of TLR4-induced inflammation was mediated by activation of CB_2 receptors (Germain et al., 2002, Correa et al., 2005, Zhao et al., 2010, Merighi et

al., 2012, Gui et al., 2013), a role for CB_1 receptors in mediating effects of some cannabinoids was also noted (Cabral et al., 2001, Esposito et al., 2001, Germain et al., 2002) and a significant proportion of studies indicated non-$CB_1/_2$ receptor mediated anti-inflammatory effects (Puffenbarger et al., 2000, Facchinetti et al., 2003a, Verhoeckx et al., 2006, Chiba et al., 2011, Ribeiro et al., 2013, Chiurchiu et al., 2014). As discussed above, it is now recognised that cannabinoids also exhibit activity at other receptor targets such as PPARs and GPR55, effects at which may underlie, at least in part, the anti-inflammatory activity of these compounds in certain cell types.

Enhancing endocannabinoid tone has been proposed as an alternative means of activating cannabinoid receptors without concomitant overt psychotropic effects associated with potent synthetic CB_1 receptor agonists. *In vitro* studies suggest that endocannabinoids elicit anti-inflammatory effects comparable to those of synthetic cannabinoids. Increasing AEA tone, either directly, via inhibition of its primary catabolic enzyme, FAAH, or by inhibiting its uptake, has been demonstrated to reduce TLR4-induced increases in the levels of pro-inflammatory cytokines and inflammatory mediators such as TNFα, IL-1β and nitric oxide, and enhance the release of the anti-inflammatory cytokine IL-10 *in vitro* [see Table 1] (Molina-Holgado et al., 1997, Puffenbarger et al., 2000, Chang et al., 2001, Facchinetti et al., 2003a, Ortega-Gutierrez et al., 2005, Tham et al., 2007, Correa et al., 2009, Correa et al., 2010). However, it should be noted that enhancing AEA tone has also been shown to enhance LPS-induced IL-6 levels in astrocytes (Ortega-Gutierrez et al., 2005), thus effects of AEA may depend on the inflammatory mediators and cell type under investigation. Similarily, enhancing 2-AG tone has also been found to induce suppressive effects on TLR4-induced immune activation, namely by reducing proinflammatory cytokines such as IL-6, TNF-α, and expression of COX2 in macrophages and glia [Table 1] (Gallily et al., 2000, Chang et al., 2001, Facchinetti et al., 2003b, Zhang and Chen, 2008). Similar to the effects observed with synthetic cannabinoids, the effects of enhancing endocannabinoid tone have been attributable to $CB_1/_2$ and non-$CB_1/_2$ receptor activation (Puffenbarger et al., 2000, Facchinetti et al., 2003a, Correa et al., 2008,

Correa et al., 2009, Correa et al., 2010, Lu et al., 2014b) [Table 1]. However, regardless of the receptor mechanism, endocannabinoids have been shown, for the most part, to inhibit TLR4-induced NFκB activation (Zhang and Chen, 2008, Correa et al., 2010, Du et al., 2011, Lu et al., 2014b). TLR4 and $CB_1/_2$ receptors share common molecular targets such as MAPK and several studies have demonstrated that this is a key pathway for endocannabinoid modulation of TLR4-induced inflammatory responses. For example, AEA has been shown to augment and attenuate LPS-induced IL-10 and IL-12p70 expression respectively, in mixed glial cultures, effects mediated by CB_2 receptor activation of ERK1/2 and JNK pathways (Correa et al., 2009, Correa et al., 2010). Similarly, AEA and 2-AG have been shown to up-regulate $CB_1/_2$ receptors and enhance IL-10 and TGFβ expression while concurrently reducing pro-inflammatory cytokine expression in primary muller glial cultures (Krishnan and Chatterjee, 2012). Thus, the anti-inflammatory effects of endocannabinoids following TLR4 activation has been proposed to be due to enhanced production of the anti-inflammatory cytokine IL-10 (Correa et al., 2010). Furthermore, it has recently been shown that AEA activation of CB_2 receptors blocks the LPS-induced reduction in CD200R1 on microglia (Hernangomez et al., 2012). Activation of CD200R1 was shown to attenuate LPS-induced pro-inflammatory and enhance IL-10 production, and IL-10 increases neuronal expression of CD200, an effect which consequently reduced neuronal cell death (Hernangomez et al., 2012). Thus, AEA-induced up regulation of CD200R1 and IL-10 expression acts to attenuate TLR4-induced microglial activation, limiting the neuroinflammatory response and inducing neuroprotection.

In vivo studies support *in vitro* data demonstrating the immunomodulatory effects of enhanced endocannabinoid tone on TLR4-mediated effects [see Table 2]. Some of the first *in vivo* data demonstrating a modulatory role for the endocannabinoid system in TLR4-induced inflammatory responses arose from our data demonstrating that systemic administration of the AEA reuptake inhibitor AM404 attenuates LPS-induced increases in plasma IL-1β and IL-6 levels (Roche et al.,

2008). However, it was also noted that LPS-induced plasma TNFα levels were augmented by systemic administration of either AM404, or the FAAH inhibitor URB597 (Roche et al., 2008). Similar augmentations in LPS-induced plasma TNFα levels were observed following central FAAH inhibition, and activation of hypothalamic CB_1 receptors was found to be critical in mediating this response (De Laurentiis et al., 2010). Thus, AEA activation of hypothalamic CB_1 receptors appears to facilitate the production and release of TNFα in the plasma in response to LPS. Hypothalamic IL-1β has been shown to mediate fever (Murakami et al., 1990) and hypophagia (Kent et al., 1994) in response to LPS, effects which can be attenuated by AEA (Hollis et al., 2011). Furthermore, recent studies from our group have demonstrated that systemic administration of the FAAH inhibitor URB597 increased AEA levels, an effect associated with the attenuation of LPS-induced IL-1β expression in the hypothalamus (Kerr et al., 2012) and CB_1 receptors have been shown to be critical in mediating the temperature response to LPS (Steiner et al., 2011; Duncan et al., 2013). Thus taken together, enhancing AEA tone, possibly via CB_1 receptor activation, attenuates TLR4-induced IL-1β expression in the hypothalamus which may in turn inhibit associated sickness behaviour.

The relatively recent development of potent and selective MAGL inhibitors such as JZL184, KLM129 and MJN110 (Long et al., 2009a, Long et al., 2009b, Chang et al., 2012, Niphakis et al., 2013, Ignatowska-Jankowska et al., 2014) has facilitated more detailed investigation of the role of 2-AG in a number of physiological and pathophysiological processes. Consistent with the *in vitro* data, enhancing 2-AG levels following MAGL inhibition also modulates peripheral and neuroinflammatory responses following TLR4 activation [Table 2], however the exact mechanisms underlying these effects remain unclear. MAGL inhibition has been shown to result in an attenuation of LPS-induced TNFα, IL-6 and MCP-1 levels in bronchoalveolar fluid (BALF) from a mouse model of acute lung injury, effects shown to be mediated by CB_1 and CB_2 receptors (Costola-de-Souza et al., 2013). Furthermore, Alhouayek and colleagues demonstrated that MAGL inhibition was associated

with a significant attenuation of colitis-induced increases in endotoxemia as measured by serum LPS levels, circulating inflammatory cytokines and the expression of TNFα and IL-1β in the liver and brain. The anti-inflammatory effects of MAGL inhibition on mucosal and peripheral inflammation was shown to be partially mediated via CB_1 and CB_2 receptors (Alhouayek et al., 2011). In a subsequent study from this group, the authors demonstrated that inhibition of 2-AG metabolising enzyme ABHD6 attenuated LPS-induced increases in IL-1β, IL-6 and MCP-1 expression in the cerebellum, lungs and liver of mice (Alhouayek et al., 2013). However, 2-AG levels were increased in the peripheral tissues, but not in the cerebellum, and only in the liver were the anti-inflammatory effects were partially attenuated by CB_1 receptor antagonism. The authors went onto conduct further studies, demonstrating that central increases in 2-AG are not responsible for the anti-inflammatory effects of ABHD6 inhibition in the brain and that these are most likely attributed to PGD_2-G (a prostaglandin D2-glycerol ester), a COX2 metabolite of 2-AG (Alhouayek et al., 2013). Thus, enhancing 2-AG tone may modulate TLR4-induced inflammation via differential mechanisms depending on the tissue in question. Similarly, Nomura and colleagues demonstrated that systemic administration of the MAGL inhibitor JZL184, enhanced 2-AG levels both centrally and peripherally and attenuated LPS-induced IL-1β, IL-1α, IL-6, TNFα, prostaglandin PGE_2 and arachidonic acid levels in the brain of mice. The central anti-inflammatory effects of MAGL inactivation were shown not to be mediated by CB_1 or CB_2 receptors, but rather attributed to a reduction in arachidonic acid and downstream prostaglandins (Nomura et al., 2011). Recent work from our laboratory further indicate that the mechanisms by which MAGL inhibition results in modulation of TLR4-induced inflammation may be different in the periphery and CNS. Our data demonstrated that systemic administration of JZL184 attenuated LPS-induced increases in cytokine expression in the rat frontal cortex and plasma, effects partially attenuated by pharmacological blockade of the CB_1 receptor (Kerr et al., 2013). However, 2-AG levels were only enhanced peripherally and central effects were not accompanied by reduced arachidonic acid and prostaglandin synthesis. Thus, the attenuation of

TLR4-induced inflammatory responses in the brain following MAGL inhibition may be mediated by modulation of peripheral systemic innate immune responses that then communicate with the CNS to induce a state of neuroinflammation. Taken together the data to date indicate that while effects of enhancing 2-AG tone on TLR4-induced inflammatory responses in the periphery may be $CB_{1/2}$ mediated, this does not appear to be the mechanism of action in the central nervous system. Such an effect may be significant, as this would allow for modulation of neuroinflammatory processes without the potential for adverse psychotropic effects that would be associated with central CB_1 receptor activation by 2-AG. Further studies are required in order to determine if this is a possible therapeutic target for neuroinflammatory disorders.

Endocannabinoid modulation of TLR3-induded inflammatory responses

Although a wealth of evidence has demonstrated a role for endocannabinoid modulation of TLR4-induced inflammation, less is known about the role of this system in the modulation of inflammatory responding to other TLRs. TLR3 receptors are found mainly in the endosomal compartments of both immune and non-immune cells where they serve to recognise double stranded RNA (dsRNA) the molecular pattern associated with viral infection (West et al., 2006). Activation of TLR3 (and also TLR4) induces a MyD88-independent signalling response. Upon ligand binding, the adaptor protein TRIF) recruits a signalling complex leading to increased transcriptional activation of interferon regulatory factor (IRF3) and late phase NFkB activation. TRIF is the main adaptor molecule in the MyD88-independent pathway and once activated forms a complex with TRAF family-member-associated NFkB activator (TANK) binding kinase 1 (TBK1) and the inhibitor of NFkB (IkB) kinase (IKK). This induces the phosphorylation of IRF3 and subsequent production of type I interferons (IFNs) which play an essential role in mediating the host's anti-viral responses and also induces late phase NFkB-inducible inflammatory genes.

TLR3 activation following systemic administration of the viral antigen polyinosinic:polycytidylic acid (poly I:C) results in enhanced production of the type I IFNs and NFkB-inducible inflammatory genes in the CNS (Cabral et al., 2001, Germain et al., 2002, Cunningham et al., 2007, Gibney et al., 2013). This enhanced neuroinflammatory profile is associated with sickness (Cunningham et al., 2007, Dantzer et al., 2011, McLinden et al., 2012, Gibney et al., 2013), anxiety- and depressive-like behaviour (Gibney et al., 2013) and has been shown to exacerbate chronic neurodegenerative processes in a model of prion disease (Field et al., 2010). Furthermore, poly I:C-induced increases in IFNβ signalling in the hippocampus have been shown to be associated with enhanced neuronal excitability (Costello and Lynch, 2013), impaired contextual and working memory (Galic et al., 2009) and seizure susceptibility (Galic et al., 2009). In addition, TLR3 deficient mice exhibit enhanced hippocampal-dependent working memory, increased hippocampal volume and neurogenesis (Okun

et al., 2010). Thus, modulation of TLR3-induced inflammatory responses may provide novel therapeutic approaches for viral-induced neuroinflammation and associated neuronal alterations.

Some of the first data demonstrating a direct role of cannabinoids in modulating TLR3-induced inflammatory responses were reported by Downer and colleagues [Table 3]. This group demonstrated that the synthetic cannabinoid receptor agonist WIN55,212-2 enhances TLR3-induced IRF3 nuclear translocation and subsequent IFNβ expression, while concurrently attenuating TLR3-induced NFκB activation and TNFα expression in astrocytes cultures. These effects are in contrast to the WIN55,212-2 induced attenuation of both IFNβ and TNFα following TLR4 activation (Downer et al., 2011). Furthermore, enhanced IFNβ was necessary for the protective effects of WIN55212-2 in a mouse model of multiple sclerosis (Downer et al., 2011). Examination of the receptor mechanisms underpinning the augmentation of IFNβ by WIN55,212-2 revealed that the effects were independent of CB_1/CB_2 receptor activation, but rather mediated by peroxisome proliferator-activated receptor (PPAR)α-induced activation of JNK, activator protein-1 and positive regulatory domain (PRD) IV and subsequent IFNβ transcriptional activation (Downer et al., 2011, Downer et al., 2012). Thus, cannabinoids appear to induce differential effects on the expression of type 1 interferons following TLR3 or TLR4 activation. However, until recently it was unknown what effect (endo)cannabinoids would have on TLR3-induced inflammatory processes *in vivo* [Table 4]. In an effort to address this question, we have recently examined the effect of the inhibition of FAAH activity on the expression of both IFN and NFkB-inducible genes in the rat hippocampus following poly I:C-induced activation of TLR3 (Henry et al., 2014). Data from this study show that systemic administration of the FAAH inhibitor URB597 increased the hippocampal expression of the type I and type II IFN, IFNα and IFNγ, respectively and IL-6, while concurrently attenuating the TLR3-induced increases in the NFkB-responsive genes, TNFα and IL-1β. Although IFNs have been shown to elicit pro-inflammatory effects and deleterious effects on neuronal function, several lines of evidence also indicate anti-inflammatory effects associated with these immune modulators. For example,

enhancement of both type 1 and 2 interferon's limits inflammation and disease progression in models of multiple sclerosis (Lin et al., 2007, Bowen and Olson, 2013, Naves et al., 2013). Thus, increasing interferon expression in combination with a reduction in pro-inflammatory cytokines may limit the neuroinflammatory cascade, at least in the hippocampus, following TLR3 activation. It should be noted that systemic administration of URB597 elicits minimal effects on TLR3-induced peripheral inflammatory responses (unpublished data) indicating that enhancing levels of AEA and related *N*-acylethanolamines elicits more profound effects on TLR3-induced neuroinflammatory responses. In order to decipher the role of FAAH substrates within the brain on TLR3-induced neuroinflammation, the effects of central administration of the FAAH inhibitor URB597 on neuroinflammatory processes following systemic TLR3 activation was also evaluated. Our findings demonstrate that selective increases in FAAH substrates in the brain elicited a potent anti-inflammatory effect, exemplified by attenuation of TLR3-induced increases in IFNγ, the IFN-inducible chemokine IP-10, the IFN regulatory gene SOCS1 and the NFkB responsive pro-inflammatory gene TNFα, with concurrent enhancement of the expression of the anti-inflammatory cytokine IL-10 (Henry et al., 2014). Thus, while systemic administration of URB597 was associated with enhanced interferon and reduced pro-inflammatory gene expression, central administration elicits a more profound attenuation of TLR3-induced pro-inflammatory genes. Although the precise molecular and receptor mechanisms underpinning FAAH substrate-induced modulation of TLR3-mediated neuroinflammatory responses remains to be determined, we propose that one possible mechanism is via increased expression of the anti-inflammatory cytokine IL-10 which in turn may act to stabilise microglia (possibly via CD200-CD200R1 interactions; (Hernangomez et al., 2012)), reducing NFκB activation and decreasing expression of pro-inflammatory cytokines and downstream mediators, thereby limiting TLR3-induced neuroinflammation.

Further indirect evidence supporting an immunoregulatory role of the endocannabinoid system on TLR3-induced inflammation is evident from studies examining the effect of Theiler's murine

encephalomyelitis virus (TMEV) which has been shown to induce an inflammatory response primarily via activation of TLR3 (So et al., 2006). To date, several studies have demonstrated that the endocannabinoid system modulates such immune responses to TMEV *in vitro* [Table 3]. Administration of AEA or the endocannabinoid reuptake inhibitor OMDM1 or UCM707 attenuates TMEV-induced IL-1β and IL-12p40 production in macrophages via CB_1/CB_2 receptor activation (Mestre et al., 2005), decreases NOS^- and TNFα release in astrocytes (Molina-Holgado et al., 1997) and VCAM-1 production in brain endothelial cells via CB_1 receptor activation (Mestre et al., 2011). Furthermore, a *in vivo* data has demonstrated that administration of the endocannabinoid transport inhibitor UCM707 reduces TMEV-induced VCAM-1 expression and microglial activation in the brain, an effect partially mediated by CB_1 receptors (Mestre et al., 2011) [Table 4]. Although Mestre and colleagues did not directly investigate or discuss the role of TLR3, given the early timepoint of pharmacological intervention it is likely that that enhancing anandamide tone may modulate TMEV-induced inflammatory responses via TLR3. Several other studies have revealed beneficial effects of endocannabinoid modulation on inflammatory and behavioural responses in the chronic phases of TMEV-induced demyelating disease, however the role of TLR3 in mediating effects at this stage is unknown (Mestre et al., 2005, Correa et al., 2011, Hernangomez et al., 2012). Taken together, the data suggest that cannabinoids (exogenous and endogenous - AEA) modulate TLR3-incuded inflammatory responses both peripherally and possible more potently in the central nervous system. This may have important implications for neurodegenerative disorders such as multiple sclerosis where enhancing IFNβ with concurrent attenuation of pro-inflammatory cytokines has been shown to be therapeutically beneficial (Javed and Reder, 2006, Severa et al., 2014). Further research is required in order to decipher the effects of modulating 2-AG and the receptor and molecular mechanisms underlying the effects of enhancing endocannabinoid tone on TLR3-induced inflammatory responses and the functional consequences of such.

Endocannabinoid modulation of inflammatory responses induced by other TLRs

A limited number of studies have examined the effects of endocannabinoid modulation on inflammatory responding following activation of TLRs other than from TLR3/4 [see Table 5]. Peptidoglycans, the main cell wall components of gram-positive bacteria, induce inflammatory processes via stimulation of TLR2 receptors. Echigo and colleagues recently reported that 2-AG suppressed TLR2-induced NFkB phosphorylation in U87MG glioblastoma cells via CB_1 receptor activation (Echigo et al., 2012) while in lymph node cells, 2-AG attenuated TLR2-induced IL-4 production via CB_2 activation (Maestroni, 2004). Thus, 2-AG may act at different receptors in different cell types in order to modulate TLR2-induced inflammatory responses. Recent data has demonstrated that the endocannabinoid/endovanilloid, N-arachidonoyl dopamine (NADA) attenuates TLR2/6-induced increases in IL-6 and IL-8 secretion, adhesion of neutrophils and the surface expression of E-selectins in human endothelial cells, effects partially mediated via a CB_1/CB_2 mechanism (Wilhelmsen et al., 2014). Although further studies are required to determine the effects of modulating AEA tone on TLR2-induced inflammatory responding, the possible receptor and molecular mechanisms involved, or effects of modulating endocannabinoid tone *in vivo*, the data so far indicate that the endocannabinoid system is capable of modulating TLR2-induced inflammation.

TLR7 and 8 recognise and are activated in response to ssRNA and thus play an important role in mediating the host's anti-viral responses. To our knowledge, only one study has examined the role of the endocannabinoid system on TLR7/8-induced immune activation (Chiurchiu et al., 2013). Pre-treatment with either AEA or the selective CB_2 receptor agonist JWH-015 attenuated TLR7/8-induced increases in pro-inflammatory cytokine release from myeloid dendritic cells (mDCs) isolated from both healthy donors and multiple sclerosis patients, effects which were completely abolished in the presence of CB_2 receptor antagonism in both cohorts (Chiurchiu et al., 2013). In contrast, pre-treatment with AEA or JWH-015 had no significant effect on TLR7/8-induced cytokine production in isolated plasmacytoid dendritic cells (pDCs) from multiple sclerosis patients. However,

it should be noted that pDCs isolated from MS patients exhibited a marked elevation in FAAH levels(Chiurchiu et al., 2013) and thus, the authors suggest that the lack of effects of AEA on TLR7/8-induced cytokine production in pDCs is due to rapid metabolism of AEA due to increased levels of FAAH. Supporting this hypothesis, the authors report that pharmacological inhibition of FAAH restored AEA-induced decreases in TNFα in TLR7/8 stimulated pDCs (Chiurchiu et al., 2013). While the effects of 2-AG, the receptor mechanisms, and effects in other cell types and *in vivo* remain to be determined, these findings demonstrate that AEA modulates TLR7/8-induced immune responses, effects which differ depending on cell type and endogenous tone of the system.

Endocannabinoid regulation of TLR-induced inflammation: possible implications for treatment of depression

The role of the innate immune system in major depressive disorder (MDD) has generated a great amount of interest over the past two decades, with increasing evidence indicating that excessive inflammation may at least be partly involved in disease pathogenesis [for detailed reviews see (Dantzer, 2006, Dantzer et al., 2008, Maes, 2011, Berk et al., 2013)]. A role of altered immune responding in MDD is supported by reports in which up to 70% of patients receiving cytokine therapy for specific cancers and malignancies develop depressive symptomatology (Musselman et al., 2001, Capuron and Miller, 2004, Capuron et al., 2004). Additionally, increases in serum and cerebrospinal (CSF) levels of pro-inflammatory cytokines (Raison et al., 2006, Dantzer et al., 2008, Dowlati et al., 2010) and a concurrent decrease in levels of the anti-inflammatory cytokine IL-10 (Dhabhar et al., 2009) has been widely reported in MDD patients. Furthermore, successful antidepressant therapy is associated with a normalisation of cytokine levels (Gazal et al., 2013), thus indicating that immune alterations may be a trait marker for MDD. Despite the wealth of data indicating altered immune functioning both basally and in response to TLR activation in MDD, there has been a lack of studies directly examining if such alterations are also associated with altered TLR expression. Recent data examining the expression of TLRs in PBMCs revealed higher expression of TLR3, 4, 5 and 7 and lower expression of TLR1 and 6 in depressed patients. Furthermore, regression analysis revealed that TLR4 expression was an independent risk factor relating to the severity of MDD (Hung et al., 2014). Additional studies have revealed that the expression of TLR3 and TLR4 mRNA is enhanced in post-mortem tissues from the dorsolateral prefrontal cortex of depressed subjects, and protein expression of these receptors increased in depressed suicide victims (Pandey et al., 2014). Similarly, preclinical studies have shown that in a stress-based model of depression, TLR4 expression in the prefrontal cortex is enhanced; effects associated with NFκB activation and enhanced iNOS and COX2 expression (Garate et al., 2014). Thus, depression appears to be

associated with alterations in central and peripheral expression of TLRs which may account for the heightened inflammatory state associated with the disorder [for excellent review of role of TLR4 in depression see (Liu et al., 2014)]. A wealth of preclinical evidence has demonstrated that activation of TLR4 is associated with depressive-like behaviour, effects attenuated by antidepressant and anti-inflammatory agents (O'Connor et al., 2009, Wang et al., 2011, Salazar et al., 2012). Similarly, recent studies have demonstrated that TLR3 activation is associated with neuroinflammation, acute sickness behaviour and prolonged depressive-like behaviour (Gibney et al., 2013). The TLR-induced neuroinflammatory cascade has been shown to modulate various glial and neuronal proteins, including increased indoleamine 2,3-dioxygenase (IDO) activation, a rate limiting enzyme in tryptophan production, reduced serotonin production and enhanced formation of the neurotoxins quinolinic acid and kynurenine. Furthermore, activation of this signalling pathway is associated with increased glutamate neurotransmission and excitotoxicity, reduced BDNF and neurogenesis, activation of neurodegenerative cascades and altered HPA axis functionality [for review (Dantzer et al., 2011, Maes, 2011, Song and Wang, 2011, Zunszain et al., 2013)]; effects may underlie pathophysiology of inflammation-associated depression. Thus, modulation of TLR-induced innate immune responses may provide a novel therapeutic target for depression, and as highlighted previously, the endocannabinoid system may provide a route towards such modulation.

In accordance, dysregulation of the endocannabinoid system has also been demonstrated in MDD. For example, CB_1 receptor density has been shown to be increased in the prefrontal cortex of depressed suicide victims (Hungund et al., 2004), while reduction in CB_1 receptor density has been reported in grey matter glia (Koethe et al., 2007). Serum levels of endocannabinoids have been reported to be reduced in patients with major depression (Hill et al., 2008). Recent studies have also indicated that genetic variations in the CB_1 and CB_2 receptor and FAAH may influence depressive symptoms and antidepressant treatment responding (Domschke et al., 2008, Onaivi et al., 2008, Juhasz et al., 2009, Monteleone et al., 2010). Similarly, genetic deletion of the FAAH or

overexpression of CB_2 receptor in mice elicits a stress-resilient (antidepressant-like) phenotype, while in comparison, CB_1 receptor knockout mice are particularly susceptible to stress-related impairments in emotional responding [see (McLaughlin and Gobbi, 2012) (Garcia-Gutierrez et al., 2010)]. Furthermore, several reports have shown stress-induced alterations in the endocannabinoid system and that modulation of the endocannabinoid function exerts anti-depressant-like effects in several animal models of depression [for detailed reviews see (Saito et al., 2010, Micale et al., 2013, Zajkowska et al., 2014)]. However, to our knowledge there have been no studies to date examining if altering TLR-associated inflammatory processes may underlie the antidepressant-like effects of endocannabinoid modulation. Indirect support of this as a possible mechanism is provided by the research demonstrating that endocannabinoids modulate TLR-induced inflammatory responding both peripherally and centrally (see earlier sections). Central CB_1 receptors are critical in mediating TLR4-induced hypothermic/fever response, HPA axis activation and enhanced circulating levels of TNFα (Steiner et al., 2011, Duncan et al., 2013) and TLR3/4 activation is known to induce depressive symptomology, an effect dependant on neuroinflammatory processes (Salazar et al., 2012, Gibney et al., 2013). Furthermore, repeated immobilisation/acoustic stress elicits a neuroinflammatory response that is mediated by TLR4 (Garate et al., 2014) and results in depressive-like behaviour (Kiank et al., 2006). Pharmacological activation of CB_1 or CB_2 receptors attenuates, while genetic deletion of these receptors augments repeated stress-induced pro-inflammatory responses and cellular oxidation in the frontal cortex (Zoppi et al., 2011, Zoppi et al., 2014) and cannabinoids attenuate the reduction in hippocampal neurogenesis and depressive-like behaviour induced by chronic stress (Segev et al., 2014, Zhong et al., 2014). Thus, while the evidence is primarily anecdotal to date with further studies required, endocannabinoid-modulation of TLR-associated neuroinflammation may provide a novel antidepressant strategy for MDD.

Endocannabinoid regulation of TLR-induced inflammation: possible implications for the treatment of schizophrenia

Schizophrenia is a chronic and debilitating psychiatric disorder affecting approximately 1% of the world's adult population. Over the last number of years there has been increased focus on the role of immune-inflammatory responses in the disease pathophysiology (Monji et al., 2009, Na et al., 2012, Bergink et al., 2014, Zakharyan and Boyajyan, 2014). In addition, a recent study has demonstrated that TLR3 and TLR4 expression is enhanced on monocytes from schizophrenic patients (Muller et al., 2012). However, conflicting data have been reported on TLR-induced inflammatory responses in schizophrenic patients. For example, Muller and colleagues demonstrated a blunted enhancement in the expression of TLR3 and TLR4 receptors, and IL-1β release following the stimulation of monocytes (Muller et al., 2012) while in comparison, McKernan et al., showed that TLR4-stimulated whole blood cultures from schizophrenic patients exhibited augmented IL-1β release when compared to controls (McKernan et al., 2011). These discrepant findings may relate to the methodological differences between the studies, however when taken together, the data suggest that schizophrenia is associated with an altered innate immune response. Further support for a possible role of TLRs in the pathogenesis of schizophrenia arises from the considerable data demonstrating that early prenatal exposure to TLR agonist's results in neuroinflammatory, neurodevelopmental and behavioural alterations in the offspring that resemble those observed in schizophrenia. Detailed consideration of the mechanisms and role of TLRs in the development of these alterations has been covered in detail elsewhere [see (Patterson, 2009, Ibi et al., 2011, Venkatasubramanian and Debnath, 2013)] and is beyond the scope of this review. However, the data indicated that anti-inflammatory and/or anti-cytokine drugs may represent novel therapeutics in psychiatric disorders including schizophrenia. Accordingly, administration of the COX-2 inhibitor celecoxib, has been shown to be associated with improvements in both positive and negative symptoms in patients suffering from first episode of schizophrenia (Muller et al., 2010), and also improved positive symptoms in patients with prolonged

schizophrenia (Akhondzadeh et al., 2007). As COX inhibitors are known to be associated with cardiovascular and gastrointestinal toxicities, alternative anti-inflammatory therapies need to be explored. So the question arises as to whether the endocannabinoid system could be a potential treatment target for schizophrenia.

Over the last number of years, there has been increased interest in the potential relationship between the endocannabinoid system and schizophrenia which has been examined in detail in a number of recent reviews (Muller-Vahl and Emrich, 2008, Fernandez-Espejo et al., 2009, Saito et al., 2013, Tan et al., 2014). Several studies have examined the interaction between exposure to potent synthetic or plant-derived cannabinoids during critical stages of development such as during adolescence, and how this may affect brain functioning and behaviour relevant to schizophrenia in vulnerable populations (double-hit theory; see (Realini et al., 2009)). However, it is unknown if exposure to cannabis (or other synthetic cananbinoids) is an independent risk factor for schizophrenia or a means of self medication. What is known though is that schizophrenia is associated with altered endocannabinoid tone, with reports of enhanced CB_1 receptor binding in the prefrontal cortex of schizophrenic patients (Dean et al., 2001, Zavitsanou et al., 2004), although studies demonstrating no change (Deng et al., 2007, Koethe et al., 2007) or a reduction in density or expression (Eggan et al., 2008, Uriguen et al., 2009, Eggan et al., 2010) have also been reported. Recent studies have indicated that schizophrenia is associated with two SNPs in the CB_2 receptor gene, mutations responsible for reduced receptor expression and functionality (Ishiguro et al., 2010), and patients with first-episode psychosis have been shown to exhibit a decreased expression of CB_2 receptors in isolated PBMCs in comparison to healthy controls (Bioque et al., 2013). Similarly, CB_2 receptor knockout mice exhibit a schizophrenia-related behavioural phenotype (Ortega-Alvaro et al., 2011). Increased levels of AEA in the CSF of patients have been shown to negatively correlate with psychotic symptoms (Giuffrida et al., 2004, Koethe et al., 2009) and schizophrenic subjects have lower post-mortem levels of AEA in the cerebellum, hippocampus and prefrontal cortex and higher

levels of 2-AG (Muguruza et al., 2013). In addition, several clinical and preclinical studies have demonstrated beneficial effects of non-selective cannabinoid receptor agonists, CB_1 receptor antagonists/inverse agonists or CB_2 receptor agonists on both positive and negative symptoms of schizophrenia [for review see (Roser and Haussleiter, 2012, Kucerova et al., 2014)]. Additionally, the antipsychotic effects of the phytocananbinoid CBD has been extensively reported in preclinical models and is currently being evaluated in a number of ongoing clinical trials [for detailed review see (Zuardi et al., 2012)]. While endocannabinoids may directly influence neuronal functioning and plasticity, modulation of immune function has been proposed as the link between cannabinoids and psychosis [for review see (Suarez-Pinilla et al., 2014)]. However, as in the case of MDD, no studies to date have examined if modulation of TLR-induced inflammation underlies the anti-psychotic effects of cannabinoids. Recent data has demonstrated a beneficial effect of CB_2 receptor agonism on MK-801-induced deficits in prepulse inhibition (Khella et al., 2014), and although the authors propose that this is likely mediated by direct CB_2-induced changes in neurotransmission, it is also likely that given the high expression of these receptors on immune cells that modulation of inflammatory process may play a role. Accordingly, we have provided an overview of the data indicating that enhancing endocannabinoid tone is associated with a decrease in TLR-induced pro-inflammatory cytokines and a concurrent increase in the anti-inflammatory cytokines such as IL-10 (see above sections). Similarly, antipsychotics are known to also modulate TLR-induced inflammation (increasing IL-10 and reducing TNFα) (Szuster-Ciesielska et al., 2004, Sugino et al., 2009) and genetic enhancement of IL-10 has been demonstrated to be associated with an attenuation of pre-pulse inhibition and latent inhibition in adult offspring of dams exposed to the TLR3 agonist poly I:C (Meyer et al., 2008). Thus, it is possible that endocannabinoid modulation of TLR-immune responses may provide a novel therapeutic target for schizophrenia.

Conclusion

Under normal physiological conditions, TLRs play a pivotal role in mediating host defences against invading pathogens and maintaining homeostasis however, aberrant or uncontrolled TLR signalling is associated with acute and chronic inflammation which may predispose or exacerbate existing disorders. Furthermore, accumulating evidence indicates that that uncontrolled TLR signalling in the CNS may underlie, at least in part, the pathophysiology of neurodegenerative and psychiatric disorders [for reviews see [(Hung et al., 2014, Pandey et al., 2014, Trotta et al., 2014)]. The studies reviewed herein demonstrate that the endocannabinoid system modulates TLR-induced inflammatory responses, with the greatest evidence supporting a role in TLR4-mediated events. The effects observed are often bi-directional, depend on the investigative conditions, the timing of modulation and the type of (endo)cannabinoid/receptor modulated. Furthermore, effects observed in studies examining endocannabinoid modulation of TLR4 immune responses cannot be generalised to those elicited by other TLRs. For example, while (endo)cannabinoids, for the most part, attenuate TLR-induced NFκB activation in a variety of experimental setting [see table 1-6], differential effects of cananbinoids are observed in relation to IRF3 activation in response to TLR3/4. The synthetic cannabinoid WIN55,212 and the FAAH inhibitor URB597 were found to augment TLR3-induced type 1 interferon expression/production, while WIN55,212 attenuated IRF3 activation in response to TLR4 activation (Downer et al., 2011, Henry et al., 2014). Furthermore, fever in response to LPS, but not poly I:C, is blocked in CB_1-/- mice, indicating a role of CB_1 receptors in mediating the hyperthermic response to TLR4, but not TLR3 activation (Duncan et al., 2013). Thus, while evidence indicated that the endocannabinoid system modulates TLR-induced inflammatory responses, further studies investigating receptor and molecular mechanism underlying the effects on TLR-induced immune responses are required. In addition, this review has highlighted the lack of direct evidence for endocannabinoid modulation of TLR-neuroinflammatory responses as a possible treatment strategy for psychiatric conditions such as MDD and schizophrenia. This is an area ripe for

further investigation, particularly given the wide array (>150 over the past decade) of cannabis-based entities in clinical trials for a variety of psychiatric and neurodegenerative disorders [International Clinical Trials Registry Platform], disorders known to have a neuroinflammatory component. Currently three synthetic cannabinoids have been licenced and are used clinically; Cesamet® (nabilone) prescribed for the relief of chemotherapy-induced nausea and vomiting, Marinol® (dronabinol; THC) for appetite stimulation and Sativex® (THC:cannabidiol) for control of cancer/neuropathic pain and spasticity in patients with multiple sclerosis. However, as these agents induce their activity via modulation of central CB_1 receptors, there is particular interest in the development of cannabinoid-based pharmaceuticals that are not associated with adverse CB_1 receptor associated psychoactive effects. Peripherally restricted CB_1 receptor agonists/antagonists have been developed and demonstrated to modulate nociceptive responding and metabolism (Cluny et al., 2010a, Cluny et al., 2010b, Yu et al., 2010), however the effects on TLR-association inflammation, peripherally or centrally, remains to be evaluated. Given the high expression of CB_2 receptors on immune cells it is not surprising that CB_2-selective agonists are considered to have multiple therapeutic applications for the relief of symptoms of neurodegenerative, immunological, and cardiovascular diseases [reviewed in (Pacher et al., 2006, Pertwee, 2012)], however global immunosupression will need to be considered in the use of these agonists. As endocannabinoids are synthesised on demand, preventing the breakdown of endocannabinoids at sites/tissues where they can elicit the most potent effects may have significant therapeutic benefit with less adverse side effects (Pertwee, 2014). Highlighted throughout this review, this approach has been shown to modulate TLR-induced inflammatory responses both peripherally and centrally, and elicit antidepressant and antipsychotic effects in several preclinical model systems (see previous sections). Of particular note was the data demonstrating that enhanced AEA tone following FAAH inhibition appears to modulate TLR-induced responses at the level of the CNS, thus possibly involving CB_1 receptor activation (Kerr et al., 2012, Henry et al., 2014). However, several lines of evidence indicate

that MAGL/ABHD6 inhibitors can potently inhibit neuroinflammatory processes in a mechanism alternate to 2-AG associated central CB_1 receptor activation (Nomura et al., 2011, Alhouayek et al., 2013, Kerr et al., 2013), thus providing a means of treating neuroinflammatory disorders that would be devoid of the potential adverse psychological effects. While this area of research is at a relatively early stage of investigation, the data to date indicate that targeting the endocannabinoid system may provide a novel and more efficacious treatment target for various diseases, in particular psychiatric and neurodegenerative conditions, where an accompanying TLR-mediated inflammatory component may be evident.

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Table 1: Endocannabinoid modulation of TLR4 responses – *in vitro* studies

Modulator	*Cell type*	*Immune/inflammatory response following TLR4 activation*	*Receptor Mechanism*	*Reference*
Direct administration of Endocannabinoids				
AEA	Human monocytic THP-1 cell line	↓ IL-1β secretion	-	(Klegeris et al., 2003)
	Human Primary muller glial cultures	↑ IL-10 & TGFβ mRNA production ↓IL-6, IL-1β, TNFα, IL-2, IFNγ, IL-15, IL-12 & IL-8 mRNA production. ↓NFκβ,MAPK activation	-	(Krishnan and Chatterjee, 2012)
	Mouse J774 macrophages	↓ NO, IL-6, PGE2 release	-	(Chang et al., 2001)
	Murine RAW 264.7 macrophages	↓ IL-12p40 promoter activity	Non CB_1/CB_2 or TRPV1	(Correa et al., 2008)
	Mouse primary mixed glial cells	↓ IL-12p35/p40 & IL-23p19 mRNA expression	-	
	Rat primary cortical microglial cells	↓ TNF-α release	Non CB_1/CB_2	(Facchinetti et al., 2003a)
	Rat primary cortical microglial cells	↓ IL-1α, IL-1β, IL-6, TNFα mRNA expression	Non CB_1/CB_2	(Puffenbarger et al., 2000)
	Rat primary cortical microglial and astrocyte cell cultures	↑ PGE_2, 8-*iso*-$PGF_{2\alpha}$ production	-	(Navarrete et al., 2009)
	Mouse primary mixed glial cultures	↓ IL-12 and IL-23 production	CB_2 mediated	(Correa et al., 2009)
	Mouse primary mixed glial cultures	↑induced IL-10 production, ↓ IkBα phosphorylation & p65 nuclear translocation	CB_2 mediated	(Correa et al., 2010)
	Mouse primary mixed glial cultures	↑ CD200R1 expression	CB_2 mediated	(Hernangomez et al., 2012)
	Mouse primary cortical mixed neuronal & glial cultures	↓LPS/IFN-γ induced neuronal death	-	
	Mouse primary cortical astrocytes	↓NO2,TNF-α release	-	(Molina-Holgado et al., 1997)
	Human primary muller glial cultures	↑ IL-10 & TGFβ mRNA production ↓IL-6, IL-1β, TNFα, IL-2, IFNγ, IL-15, IL-12. ↑ IL-8 mRNA production. ↓NFκβ activation		(Krishnan and Chatterjee, 2012)

2-AG	Mouse J774 macrophages	↓ IL-6 and ↑ induced NO release	-	(Chang et al., 2001)
	Mouse peritoneal macrophages	↓ TNFα levels	-	(Gallily et al., 2000)
	Rat primary cortical microglial cells	↓ TNFα release	Non CB_1/CB_2 mediated	(Facchinetti et al., 2003a)
	Rat primary hippocampal neurons	↓ IL-1β-induced COX2 expression	CB_1 mediated	(Zhang and Chen, 2008)
	Rat primary astroglial cultures	↓ COX2 expression		
	Mixed hippocampal neuronal & astroglial cultures			
	Rat primary caudate nucleus neurons	↓ COX2 levels, ↓ pNFkB, pERK1/2 & p-P38 MAPK	CB_1 mediated	(Lu et al., 2014a)
	Mouse primary hippocampal neurons	↓ COX2 expression & NFκB p65 phosphorylation	CB_1 and PPARγ. mediated	(Du et al., 2011)
	Mouse J774 macrophages	↓IL-1β mRNA, NO production	Non CB_1/CB_2	(Alhouayek et al., 2013)
Endocannabinoid modulators (metabolic enzyme inhibitors)				
URB597 (FAAH inhibitor)	Rat primary microglial cultures	↓ COX2 expression , iNOS, PGE2 , NO & TNFα release	Non CB_1/CB_2 mediated	(Tham et al., 2007)
UCM707 (FAAH inhibitor)	Rat primary astrocyte cultures	↓ iNOS expression, NO levels ↓TNFα, IL-1β & ↑ IL-6 production	CB_1/CB_2 mediated	(Ortega-Gutierrez et al., 2005)
JZL184 URB602 (MAGL inhibitors)	Mouse primary hippocampal neurons	↓ COX2 expression & NFκB p65 phosphorylation	CB1 and PPARγ. mediated	(Du et al., 2011)
WWL70 (ABHD6 inhibitor)	Mouse J774 macrophages Thioglycolate-elicited peritoneal macrophages (TGEM) BV2 microglial-like cells	↓IL-1β, PGD_2, PGJ_2, PGE_2 in J774 cells ↓IL-1β in TGEM and BV2 cells	Non CB_1/CB_2	(Alhouayek et al., 2013)

Table 2: *Endocannabinoid modulation of TLR4 responses – in vivo studies*

Modulator	*Response following TLR4 activation*	*Receptor Mechanism*	*Reference*
Direct administration of Endocannabinoids			
AEA (1mg/kg s.c. rat)	↓ LPS induced fever, and hypophagia ↓ LPS-induced Fos expression in the hypothalamus	-	(Hollis et al., 2011)
AEA (50ug/5µl icv rat)	↑ LPS- induced hypothermic response	Possible CB_1 mediated	(Steiner et al., 2011)
2-AG (3mg/kg i.p. mice)	↓LPS induced COX2 levels in hippocampus	CB_1 mediated	(Zhang and Chen, 2008)
FAAH inhibitors			
URB597 (50ng/5ul i.c.v. rat)	↑ LPS-induced plasma TNFα and Oxytocin	CB_1 mediated	(De Laurentiis et al., 2010)
URB597 (0.3-0.6mg/kg i.p. rat)	↓LPS-induced increase in leukocyte adhesion in intestinal venules ↑ functional capillary density	Leukocyte adhesion CB_2 mediated	(Kianian et al., 2013)
URB597 (1mg/kg i.p. rat)	↓LPS-induced IL-1β, SOCS3 expression in hypothalamus	-	(Kerr et al., 2012)
URB597 (0.6mg/kg i.p. rat)	↑ LPS induced plasma TNFα	-	(Roche et al., 2008)
URB597 (0.6mg/kg i.v. mouse)	↓ LPS-induced leukocyte adhesion in intestinal V1 & V3 venules	-	(Sardinha et al., 2014)
MAGL/ABHD6 inhibitors			
JZL184 (16mg/kg i.v. mice)	↓ LPS-induced leukocyte adhesion in intestinal V1 & V3 venules	-	(Sardinha et al., 2014)
JZL184 (10mg/kg i.p. rat)	↓LPS-induced IL-1β, IL-6,TNF-α, IL-10 expression in FC . ↓LPS-induced TNF-α, IL-10 levels in plasma	↓in IL-1β in cortex CB_1 mediated. ↓in TNF-α, IL-10 in plasma CB_1 mediated.	(Kerr et al., 2013)
JZL184 (40mg/kg i.p. mouse)	↓LPS-induced IL-1β, IL-1α, IL-6, TNFα, PGE2 levels in brain	Non CB_1/CB_2	(Nomura et al., 2011)

JZL184 (16mg/kg i.p. mouse)	↓ LPS induced leukocyte count, TNFα, IL-6, MCP-1 levels in Bronchoalveolar lavage fluid (BALF) ↓LPS-induced lung damage	CB_1 and CB_2 mediated	(Costola-de-Souza et al., 2013)
WWL70 (20mg/kg i.p. mice)	↓IL-1, IL-6 expression in cerebellum, lung and liver	Effects in liver CB_1 mediated	(Alhouayek et al., 2013)
Endocannabinoid re-uptake inhibitor			
AM404 (20mg/kg i.p. rat)	↑ plasma TNFα levels ↓ plasma IL-1β, IL-6 levels	↓IL-1β is CB_1 mediated	(Roche et al., 2008)

Table 3: Endocannabinoid/cannabinoid modulation of TLR3-induced immune responses: i*n vitro* studies

Modulator	Cell type	Response following polyi:c-induced TLR3 activation	Receptor	Reference
WIN55-212,2	TLR3 expressing Human Embryonic Kidney (HEK) 293 cells	↓ NFkB, TNFα ↑IRF3 translocation and activation	Non CB_1/CB_2 PPARα mediated	(Downer et al., 2011) (Downer et al., 2012)
	Mouse bone marrow-derived macrophages	↑ IFNβ expression		
	Human U373 astrocytoma cells	↓ NFkB, TNFα, ↑ IFNβ expression		
	Mouse primary astrocytes	↓ NFkB, TNFα, ↑ IFNβ expression, ↑ nuclear translocation of IRF3		
		Response following TMEV exposure		
AEA	Mouse macrophage cultures	↓ IL-1β & IL-12p40 production	-	(Mestre et al., 2005)
	Mouse primary cortical astrocytes	↓ NO & TNFα release	-	(Molina-Holgado et al., 1997)
	Mouse primary astrocytes	↑ IL-6 release	CB_1 mediated	(Molina-Holgado et al., 1998)
	Mouse primary mixed glial cultures	↓ IL-12p70, IL-23 & ↑ IL-10 production	CB_2 mediated	(Correa et al., 2011)
	Mouse endothelial & astrocyte co-cultures	↓ VCAM-1 production & leukocyte adhesion	CB_1 mediated	(Mestre et al., 2011)
OMDM1 (EC reuptake inhibitor)	Mouse Macrophage cultures	↓ IL-1β & IL-12p40 production	-	(Mestre et al., 2005)
WIN55-212,2	Mouse endothelial & astrocyte co-cultures	↑ COX2 expression & PGE2 release	Non CB_1/CB_2 or TRPV1	(Mestre et al., 2006)
		↓ VCAM-1	PPARγ mediated	(Mestre et al., 2009)

Table 4. Endocannabinoid modulation of TLR3-induced immune responses: *in vivo studies*

Modulator	Immune response in following TLR3 activation	Receptor	Reference
URB597 (1mg/kg., i.p. rat)	↑ hippocampal expression of IFNα, IFNγ, IL-6; ↓TNFα & IL-1β	-	(Henry et al., 2014)
URB597 (50ug., *i.c.v.rat*)	↓ hippocampal expression of TNFα, IL-1β & ↑ IL-10 ↓IRF7, IFN-γ, IP-10 & SOCS1	-	(Henry et al., 2014)
Modulator	**Immune response in TMEV-infected mice**	**Receptor**	**Reference**
UCM707 (3mg/kg., i.p. b.i.d. 3 days)	↓ VCAM-1 expression in cortex ↓ microglial activation	Partial CB_1 receptor	(Mestre et al., 2011)

Table 5. Endocannabinoid/cannabinoid modulation of other TLR-induced immune mediators

Modulator	Species/cell type	Immune/inflammatory response following TLR activation	Receptor Mechanism	Reference
2-AG (50µM i.d.)	Mouse	↓ TLR2-induced IL-4 production in draining lymph node cells	CB_2 mediated	(Maestroni, 2004)
2-AG	Human glioblastoma U87MG cell line	↓ TLR2-induced NFkB	CB_1 mediated	(Echigo et al., 2012)
AEA	Human PBMCs	↓ TLR7/8-induced TNFα, IL-6 & IL-12p40	-	(Chiurchiu et al., 2013)
NADA	Human lung microvascular endothelial cells	↓ TLR2/6-induced IL-6 & IL8	-	(Wilhelmsen et al., 2014)
WIN55,212-2		↓ TLR2/6-induced IL-6, IL-8 & neutrophil adhesion	-	(Wilhelmsen et al., 2014)
JWH-015	Human PBMCs	↓ TLR7/8-induced TNFα, IL-6 & IL-12p40	CB_2 mediated	(Chiurchiu et al., 2013)

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