Pharmacology & Therapeutics 163 (2016) 82–93

Contents lists available at ScienceDirect

Pharmacology & Therapeutics

journal homepage: www.elsevier.com/locate/pharmthera

Associate editor: D. Hoyer

Antidepressant therapies inhibit inflammation and microglial M1-polarization

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ARTICLE INFO

Available online 18 April 2016

Keywords:
Interferon-α
Nicotinic acetylcholine receptor α7
Interferon regulatory factor-5
Cyclic AMP response element-binding protein
Glycogen synthase kinase-3β
Respiratory burst

ABSTRACT

Macrophages and their counterparts in the central nervous system, the microglia, detect and subsequently clear microbial pathogens and injured tissue. These phagocytic cells alter and adapt their phenotype depending on their prime activity, i.e., whether they participate in acute defence against pathogenic organisms ('M1'-phenotype) or in clearing damaged tissues and performing repair activities ('M2'-phenotype). Stimulation of pattern recognition receptors by viruses (vaccines), bacterial membrane components (e.g., LPS), alcohol, or long-chain saturated fatty acids promotes M1-polarization. Vaccine or LPS administration to healthy human subjects can result in sickness symptoms and low mood. Alcohol abuse and abdominal obesity are recognized as risk factors for depression. In the M1-polarized form, microglia and macrophages generate reactive oxygen and nitrogen radicals to eradicate microbial pathogens. Inadvertently, also tetrahydrobiopterin (BH4) may become oxidized. This is an irreversible reaction that generates neopterin, a recognized biomarker for depression. BH4 is a critical cofactor for the synthesis of dopamine, noradrenaline, and serotonin, and its loss could explain some of the symptoms of depression. Based on these aspects, the suppression of M1-polarization would limit the inadvertent catabolism of BH4. In the current review, we evaluate the evidence that antidepressant treatments (monoamine reuptake inhibitors, PDE4 inhibitors, lithium, valproate, agomelatine, tianeptine, electroconvulsive shock, and vagus nerve stimulation) inhibit LPS-induced microglia/macrophage M1-polarization. Consequently, we propose that supplementation with BH4 could limit the reduction in central monoamine synthesis and might represent an effective treatment for depressed mood.

Contents

1. Introduction

The innate immune system responds both to microbial pathogens and to injured tissue (Iwasaki & Medzhitov, 2015). Macrophages, as well as their counterparts in the central nervous system, the microglia, are essential components of the innate immune system (Benoit et al., 2008; Dantzer et al., 2008; Kettenmann et al., 2011). They alter and adapt their phenotype depending on their prime activity, i.e., whether

Abbreviations: 5HT, serotonin; BH4, tetrahydrobiopterin; CBP, CREB-binding protein; CREB, cAMP response element-binding protein; DA, dopamine; ECT, electroconvulsive shock therapy; GR, glucocorticoid-receptor; GSK3 β, glycogen synthase kinase-3β; HAT, histone acetyltransferase; HDAC, histone-deacetylase; IDO, indoleamine 2,3-dioxygenase; IFNα, interferon-α; IRF5, interferon-regulated factor-5; LPS, lipopolysaccharide; MAOI, monoamine-oxidase inhibitor; NA, noradrenaline; nAChR, nicotinic acetylcholine receptor; NOD, nucleotide-binding oligomerization domain-containing proteins; PBMC, peripheral blood mononuclear cell; PDE, phosphodiesterase; PGE2, prostaglandin E2; PKB, protein kinase-B; PRR, pattern recognition receptor; SWS, slow-wave sleep; TCA, tricyclic antidepressants; TLR, toll-like receptor.

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http://dx.doi.org/10.1016/j.pharmthera.2016.04.001
0163-7258/

they participate in normal surveillance (sometimes referred to as 'resting'), contribute to acute defence against pathogenic organisms ('activated' or 'M1'-phenotype), or whether they clear damaged tissue and perform repair activities ('M2'-phenotype, 'alternatively activated') (Bystrom et al., 2008; Ransohoff & Perry, 2009; Saijo & Glass, 2011; Boche et al., 2013). Stress, which is an important risk factor for depression, causes phenotypic changes in phagocytic cells that resemble the acute microbial defence state (Kubera et al., 2011). By contrast, many of the currently used antidepressant therapies (compounds, as well as procedures) provoke alterations in macrophage/microglia function that reflect a getaway from the M1-phenotype. In the current review, we summarize the mechanisms for M1-polarization by pro- and antidepressant principles. Pharmacological principles that either prevent M1-polarization or promote M2- and resting states could represent starting points for novel types of antidepressants. Finally, we will reflect on how M1-polarization could result in depressed mood.

2. Macrophages and microglia as part of the innate immune system

The innate immune system is the first line of host defence during infection and provides a rapid response to microbial pathogens and injured tissue (Medzhitov & Janeway, 1998; Magor & Magor, 2001). The adaptive immune system, on the other hand, is responsible for elimination of pathogens in later phases of infection (Mogensen, 2009). Phagocytic cells (macrophages in the periphery and microglia in the central nervous system) represent an essential component of the innate immune system (Mosser & Edwards, 2008; Mogensen, 2009). Macrophages and microglia recognize chemical structures that are present in various classes of microbes, but absent on host cells, as well as structures found in stressed, dying or dead host cells (Mogensen, 2009). Phagocytic cells recognize these chemical structures via special receptors expressed on the cell surface, endosomes, lysosomes, and in the cytosol (Kumar et al., 2011; Iwasaki & Medzhitov, 2015). Among these so-called 'pattern recognition receptors', the Toll-like receptors (TLRs) and the nucleotide-binding oligomerization domain-containing proteins (NOD receptors) are the ones that have been most extensively investigated (Jack et al., 2005; Mogensen, 2009; Correa et al., 2012). TLRs and NODs activate intracellular signaling pathways that result in inflammation, immediate antimicrobial activity and stimulation of the adaptive immune system (Mogensen, 2009). This involves transcription and release of inflammatory cytokines, chemokines and antiviral interferons. Furthermore, these intracellular pathways increase the transcription of enzymes that limit the growth of pathogens. Examples are the enzyme indoleamine 2,3-dioxygenase (IDO), which promotes depletion of the essential amino acid tryptophan, or enzymes that are required for generation of oxidative radicals that oxidize microbial RNA, DNA, and unsaturated fatty acids (Benoit et al., 2008). Macrophages and microglia cells thus act both as 'sensors' of infection and as 'effectors' by generating antimicrobial activity.

There is a common design principle to the responses of the immune system. The first set of cells that sense infection produce one set of cytokines (level-1 cytokines: IL1β, IL12, IL23, IL6, INFα, and IFNβ) to induce specific lymphocytes, which in turn produce a second set of cytokines (level-2 cytokines) (Iwasaki & Medzhitov, 2015). Level-2 cytokines (IFNγ, IL17, and IL21) activate effector cells (Saijo & Glass, 2011; Chhor et al., 2013; Iwasaki & Medzhitov, 2015). Notably, parasitic worms and allergens are not recognized by pattern recognition receptors (PRRs). Yet the innate immune system is able to detect these pathogens through recognition of *functional* features (e.g., pore formation and disruption of basement membranes, or sensing of enzymatic activities caused by pathogen-excreted cysteine proteases). It should be noted that such responses also occur after infection by PRR-activating microbes. However, different kinds of immune responses are induced depending on whether the presence of the pathogen is detected by functional features only (parasitic worms), or by a *combination* of structural and functional features (viruses, bacteria, fungi) (Iwasaki & Medzhitov, 2015). The activation of PRRs may produce fierce 'type-1' immune responses, including production of cytotoxic oxygen radicals. By contrast, the 'type-2' immune response to parasitic worms resembles in many ways a form of tissue-repair (including the induction of 'alternatively activated' M2-macrophages) (Boche et al., 2013; Cherry et al., 2014; Hu et al., 2015; Iwasaki & Medzhitov, 2015).

2.1. Macrophages and microglia cells adapt their phenotype in response to extrinsic cues

Microglia and macrophages are derived from different lineages (Ginhoux et al., 2013; Prinz & Priller, 2014). Despite their different ontogeny, microglia and macrophages share a variety of features under M1 polarizing conditions (Durafourt et al., 2012). For example, microglia, like macrophages, express a full set of pattern recognition receptors (TLRs, NODs, NOD-like receptors, scavengers) and produce level-1 cytokines IL1β, TNFα, and IL6 (Cherry et al., 2014).

In the surveillance mode, microglia and macrophages exhibit small cell bodies and thin processes that branch several times. Once a danger signal is encountered, phagocytic cells attain a pro-inflammatory M1 phenotype that is characterized by hypertrophic bodies with shorter, fewer, and thicker processes. Following M1-polarization, these cells often progress towards a repairing stage (the 'alternative' or M2 phase). Here cells display hypertrophic cell bodies with ramified processes and high phagocytic capacity. The activation and phenotypic alteration of macrophages and microglia were shown to be rapid and reversible (Benoit et al., 2008; Mosser & Edwards, 2008; Cherry et al., 2014).

Resting macrophages and microglia respond to pathogen detection by acquiring an activated state (for review see (Hu et al., 2015). Their common response involves an up-regulation of level-1 cytokines (IL1β, TNFα, IL6, IL12), cytokine receptors (IL17R, IL15RA), chemokines (CCL2, CCL5 and CXCL8), and the chemokine receptor CCR7 (Benoit et al., 2008). It should be noted that several level-2 cytokines and other mediators modify the activation state (Fig. 1). For instance, level-2 cytokines of the type-2 immune response (IL4, IL5, IL13) create a phenotype that is sometimes described as 'M2A', while the anti-inflammatory cytokine IL10 and corticosteroids induce an 'M2C'-phenotype (Benoit et al., 2008; Chhor et al., 2013). When PRR-activated macrophages or microglia cells are co-stimulated by a level-2 cytokine of the type-1 immune response (e.g., IFNγ or IL17), the cells assume a classically activated 'M1'-phenotype and mount a fierce antimicrobial response (Saijo & Glass, 2011; Iwasaki & Medzhitov, 2015). To complete this section, TLR agonists and immune complexes are reported to induce a 'M2B' phenotype (Chhor et al., 2013; Perry & Teeling, 2013). Thus, whereas the M1 phenotype is specialized to eradicate pathogens and is well defined, the definition and characterization of the repair-promoting M2-phenotypes is relatively ambiguous, and for that reason, the subdivision of M2-phenotypes is no longer considered appropriate (Sica & Mantovani, 2012).

3. Activation of the innate immune system by risk factors for depression

3.1. Immune challenge with lipopolysaccharide or interferon-α signal to interferon-regulated factor-5 and cause macrophage-polarization

Lipopolysaccharide (LPS) is a component of the cell membrane of Gram-negative bacteria like *Escherichia coli* or *Salmonella* subspecies. Systemically applied LPS activates the innate immune system via stimulation of the pattern recognition receptor TLR4 (Jack et al., 2005; Mogensen, 2009) and provokes the release of early cytokines (IL1β, TNFα, IL6) that are characteristic for a bacterial type-1 immune response (Benoit et al., 2008; Mogensen, 2009; DellaGioia & Hannestad, 2010; Kumar et al., 2011). In healthy human volunteers, a challenge dose of LPS frequently results in the occurrence of depressive symptoms (for a review, see DellaGioia & Hannestad, 2010; Slavich & Irwin, 2014).