Progress in Neurobiology xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Progress in Neurobiology

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

Review article

The endocannabinoid system and its therapeutic exploitation in multiple sclerosis: Clues for other neuroinflammatory diseases

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ARTICLE INFO

Article history:
Received 29 April 2017
Received in revised form 23 October 2017
Accepted 28 October 2017
Available online xxx

Keywords:
Cannabinoid
Clinical trials
Endogenous lipids
Inflammation
Neurodegeneration
Neurotransmission

ABSTRACT

Multiple sclerosis is the most common inflammatory demyelinating disease of the central nervous system, caused by an autoimmune response against myelin that eventually leads to progressive neurodegeneration and disability. Although the knowledge on its underlying neurobiological mechanisms has considerably improved, there is a still unmet need for new treatment options, especially for the progressive forms of the disease. Both preclinical and clinical data suggest that cannabinoids, derived from the *Cannabis sativa* plant, may be used to control symptoms such as spasticity and chronic pain, whereas only preclinical data indicate that these compounds and their endogenous counterparts, i.e. the endocannabinoids, may also exert neuroprotective effects and slow down disease progression. Here, we review the preclinical and clinical studies that could explain the therapeutic action of cannabinoid-based medicines, as well as the medical potential of modulating endocannabinoid signaling in multiple sclerosis, with a link to other neuroinflammatory disorders that share common hallmarks and pathogenetic features.

Contents

Abbreviations: 2-AG, 2-arachidonoylglycerol; Aβ, β-amyloid; GABA, γ-amino butyric acid; AD, Alzheimer's diseases; ALS, amyotrophic lateral sclerosis; AEA, anandamide; EAE, autoimmune encephalomyelitis; BBB, blood brain barrier; CDB, cannabidiol; CB, cannabinoid receptor; CNS, central nervous system; COX, cyclooxygenase; DAGL, diacylglycerol lipase; CB, endocannabinoids; FAAH, fatty acid amide hydrolase; HD, Huntington's disease; IFN, interferon; IL, interleukin; MS, multiple sclerosis; MAGL, monoacylglycerol lipase; NAPE-PLD, *N*-acylphosphatidyl-ethanolamine-specific phospholipase D; PD, Parkinson's disease; PPAR, peroxisome proliferator-activated receptors; PP, primary progressive; PR, progressive relapsing; RR, relapsing-remitting; MRI, resonance imaging; SP, secondary progressive; SOD, superoxide dismutase; THC, tetrahydrocannabinol; Th, -helper; TRPV 1, transient receptor potential vanilloid 1; TNF, tumour necrosis factor.

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https://doi.org/10.1016/j.pneurobio.2017.10.007

1. Introduction to neuroinflammation and multiple sclerosis

Although the central nervous system (CNS) has been long considered an immune-privileged site, mainly due to the presence of the blood brain barrier (BBB), immune activities occur and are sometimes ncesessary for neuronal function and host defence (Banks, 2015). Any insult of the brain is associated with acute inflammation, characterized by endothelial cell activation, tissue oedema and release of inflammatory mediators that provide to eliminate the insult and restore brain function. However, neuroinflammation is widely regarded as a chronic process that involves both sustained activation of resident glial cells (microglia and astroglia) and recurrent infiltration of peripheral leukocytes and soluble inflammatory mediators. Microglial cells, either derived from mesenchymal monocyte precursors of the mesoderm or from non-hematopoietic microglial precursors in the yolk sac, both entering the brain during embryonic and fetal stages, are the immune sentinels of the CNS. Microglial cells are extremely heterogeneous, because they can exist in many different forms and activation states, from neuro-protective to neuro-destructive (Nayak et al., 2014). Microglial cells are critical for the development and surveillance of the CNS, shaping the immune phenotype of the brain and critically modulating neuroinflammation (Mosser et al., 2017). Astrocytes are by far the most abundant cells in the CNS, where they regulate virtually every physiological process, from physically forming the BBB and giving nutritional support to sustaining neurotransmitters turnover, synaptic plasticity and immune functions. Indeed, immune activation of astrocytes in response to signals released by injured neurons or activated microglia leads to the so-called astrogliosis, a hallmark of neuroinflammation, which leads to glial scars that prevent axonal regeneration (Jensen et al., 2013). During neuroinflammation also immune cells of both innate (monocytes/macrophages and dendritic cells) and adaptive (T and B lymphocytes) immunity are persistently recruited to the brain, and release inflammatory cytokines and chemokines that exacerbate neuroinflammation (Schwartz and Baruch, 2014). As a matter of fact, neuroinflammation often may lead to neurodegeneration, axonal loss and synaptic dysfunction, and thus it is typically associated with several neurological disorders, of which multiple sclerosis (MS) is the prototypical example. MS is a progressive, chronic neurodegenerative disease, which affects approximately 2.3 million people worldwide (Browne et al., 2014). It is the most common neurological disorder in young adults, and is regarded as an autoimmune disease in which inflammation leads to demyelination of the axons in the CNS. Although the aetiology of MS is still unknown, it is almost unanimously believed that both genetic and environmental components play a central role in disease onset and development (Hafler et al., 2007; Huynh and Casaccia, 2013). The MS prevalence ratio of women to men (2.3–3.5:1) has increased markedly during the last decades and this rapid increase probably reflects a differential gender response to unidentified changes in environment or nutrition (Harbo et al., 2013). MS is characterized by a series of episodic acute attacks (referred to as relapses) and remissions, but it gradually leads to progressive neurodegeneration and deterioration of neurologic function without any further remission. Although the different clinical courses of MS (also called “types” or “phenotypes”) were defined in 1996, the International Advisory Commette on Clinical Trials of MS, based on advances in the understanding of the disease process in MS and MRI technology, classified MS into only four independent subtypes: (i) relapsing-remitting (RR), defined by unpredictable relapses with full recovery or with sequelae; (ii) primary progressive (PP), which progresses continuously from the onset without attacks; (iii) secondary progressive (SP), which follows initial RR and then progresses with decline without remissions; and (iv) progressive relapsing (PR), characterized by a steady decline onset with superimposed attacks (Fig. 1). The RR-MS is the most prevalent form and accounts for approximately 85% of all cases (Compston and Coles, 2008; Lublin et al., 2014). However, the Committee also recognized the clinically isolated syndrome (CIS) as a first episode of neurologic symptoms caused by inflammation and demyelination that must last at least 214 h and that is characteristic of MS even though does not yet meet the criteria for its diagnosis because patients with CIS might also not end up developing MS (Lublin et al., 2014). MS pathogenesis and pathophysiology have been extensively studied, especially in the experimental autoimmune encephalomyelitis (EAE) mouse model, and are thought to involve initially the disruption of the immune system and of central myelin-producing cells. In the course of MS, damage to the BBB and over-activation of brain microglia lead to a substantial infiltration of autoreactive lymphocytes, causing oligodendrocyte death and axonal damage and ultimately resulting in demyelination, synaptic alteration and neuronal loss (Compston and Coles, 2008; Dutta and Trapp, 2011; Calabrese et al., 2015; Mahad et al., 2015) (Fig. 2).

Though the immune-mediated neuroinflammation hypothesis has dominated MS research for over 50 years, recent evidence seems to point to a neurodegenerative and microglia-centered process, according to which MS is primarily a neurodegenerative disease that starts in the brain, and then develops because of inflammation (Kassmann et al., 2007; Lassmann et al., 2012). This has led to the current “inside-out” and “outside-in” models of MS immunopathogenesis, whereby in the first model the immune response that destroys myelin and leads to BBB breakdown is driven by a dysfunction of brain cells, whereas in the second model a dysfunction residing in the periphery leads to BBB damage, myelin disruption and axonal death (Tsunoda and Fujinami, 2002; Stys et al., 2012).

The immune-mediated attacks are mainly driven by cells of adaptive immunity, namely myelin-specific and self-reactive CD8 amd CD4 T-cells (T-helper 1 and T-helper 17), with a key contribution of B-cells that produce high levels of autoantibodies and that have been recently shown to contribute to neurodegeneration and cortical demyelination, especially for meningeal ectopic B cell follicles (Fraussen et al., 2016). During these attacks, the myelin sheath is damaged, thus impairing axonal conduction and the correct communication between different parts of the nervous system (Compston and Coles, 2008; Gandhi et al., 2010; Mahad et al., 2015). These processes are sustained by a subsequent recruitment of cells of the innate immunity from the periphery that further amplify the activation of pathogenic T-cells and the destruction of neurons and oligodendrocytes. In addition, there is a permanent activation of resident microglia and astrocytes that further potentiate the neuroinflammatory response by producing proinflammatory mediators (Gandhi et al., 2010; Chiurchiù, 2014) (Fig. 2). Oligodendrocytes are responsible for myelin production

Please cite this article in press as: V. Chiurchiù, et al., The endocannabinoid system and its therapeutic exploitation in multiple sclerosis: Clues for other neuroinflammatory diseases, Prog. Neurobiol. (2017), https://doi.org/10.1016/j.pneurobio.2017.10.007