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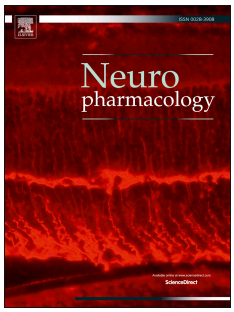

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Toll-like Receptor Signalling as a Cannabinoid Target in Multiple Sclerosis

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Abstract

Toll-like receptors (TLRs) are the sensors of pathogen-associated molecules that trigger tailored innate immune intracellular signalling responses to initiate innate immune reactions. Data from the experimental autoimmune encephalomyelitis (EAE) model indicates that TLR signalling machinery is a pivotal player in the development of murine EAE. To compound this, data from human studies indicate that complex interplay exists between TLR signalling and Multiple Sclerosis (MS) pathogenesis. Cannabis-based therapies are in clinical development for the management of a variety of medical conditions, including MS. In particular Sativex®, a combination of plant-derived cannabinoids, is an oromucosal spray with efficacy in MS patients, particularly those with neuropathic pain and spasticity. Despite this, the precise cellular and molecular mechanisms of action of Sativex® in MS patients remains unclear. This review will highlight evidence that novel interplay exists between the TLR and cannabinoid systems, both centrally and peripherally, with relevance to the pathogenesis of MS.

Keywords:

Multiple Sclerosis; cannabinoids; cell signalling; innate immunity; toll-like receptor; therapeutics

1. Introduction

Multiple Sclerosis (MS) is a chronic inflammatory autoimmune condition of the central nervous system (CNS) characterized by inflammatory episodes (relapses) that damage CNS myelin leading to neuronal dysfunction and a broad spectrum of neurological symptoms (Weiner, 2008). Hallmarks of the disease include demyelination, axonal loss, inflammation and gliosis (Bruck, 2005). Both the grey and white matter of the CNS are affected with concomitant cell death of neurons and axons (Vosoughi and Freedman, 2010). Common symptomology in the disease are diverse, and include spasticity (often associated with hyper-reflexia, muscle weakness and loss of dexterity), diplopia, bowel/bladder dysfunction, fatigue and cognitive disturbances (Gaby, 2013). MS is more common in women than men with a ratio of 2:1 observed, and the illness usually manifests in patients between the ages of 20 and 40 years, but cases have been reported at all stages of life (Popescu, 2014). It is estimated that more than 2 million people worldwide suffer from MS, and currently it is the primary cause of neurological disability in young adults (O'Connell et al., 2014).

Autoimmunity drives the development of MS, and both innate and adaptive arms of the immune system are pivotal in the progression of disease. The innate immune system is intricately controlled by a number of cell types including