FDA-Approved Multiple Sclerosis Drugs

The molecular effects of traditional and more recently FDA-approved Multiple Sclerosis (MS) drugs on four CNS cell types.

1. Introduction

MS is an inflammatory disease of the central nervous system (CNS) characterized by oligodendrocyte pathology, microgliosis, astrogliosis, alterations of the blood–brain barrier (BBB), demyelination and neurodegeneration, and an exacerbating infiltration of both innate and adaptive immune cells into the brain [1][2]. MS is a complex disease with a large heterogeneity in MS lesions [3][4]. Furthermore, the non-lesioned white- and grey-matter regions in MS brains are different from those in healthy individuals [2][3]. For quite some time, the dysregulation of the peripheral immune system, causing immune cells infiltrating the CNS, autoreactivity against myelin sheath components and secondary BBB dysfunction, has been considered to be the primary cause of MS CNS pathology, defined as the outside-in hypothesis [5]. However, more recent research on MS and other neurodegenerative diseases has indicated a central role for a distinct type of macrophage found in the CNS, the microglia [6][7]. The hypothesis in which MS pathology is first and foremost caused by CNS-intrinsic factors, subsequently leading to the infiltration of peripheral immune cells via a leaking BBB, represents the inside-out model [8][9], which is supported by pathological evidence showing the absence of peripheral immune cells in newly forming MS lesions [10].

Because the outside-in model has been the norm for a long time, the currently available MS drugs approved by the Food and Drug Administration (FDA) have been mainly designed to target various cell types within the peripheral immune system [11] and most drug-impact studies have been directed towards their peripheral effects on the cells of the adaptive immune system [12]. However, it is likely that the MS drugs also affect (innate) CNS cells and the molecular cascades associated with neuroinflammation, since most genes that are dysregulated in MS-peripheral immune cells are also expressed in microglia [13]. MS drug effects on CNS pathology have been mostly studied in humans and animals on the basis of the clinical features of disease progression, magnetic resonance imaging (MRI) measures, and blood or cerebrospinal fluid (CSF) levels of biomarkers for demyelination and neuronal degeneration [14][15][16]. For this reason, we set out to review studies assessing at the molecular level, the effects of MS drugs on the pathways operational in CNS cells.

Molecular effects on cell types in the CNS have been reviewed for a number of FDA-approved MS drugs, such as Fingolimod (FTY720; Gilenya), Dimethyl Fumarate (DMF; Tecfidera), Glatiramer Acetate (GA; Copaxone), Interferon-beta (IFN-β; Rebif, Avonex, Betaseron, Extavia, Plegridy) and Teriflunomide (TF; Aubagio) [17][18][19][20][21][22][23][24][25][26][27][28]. The CNS-directed molecular effects of more recently approved drugs, such as Laquinimod (LQ; Nerventra), Natalizumab (NZ; Tysabri), Alemtuzumab (AZ; Lemtrada) and Orcelizumab (OCR; Ocrevus), have been less well described, except for the neuroprotective effects of LQ and NZ [29][30][31]. In general, each of these previous studies has reported the (molecular) effects of only one or two MS drugs (e.g., [28][29][31]) on one or two CNS cell types (e.g., [22]). Moreover, the protective effects of MS drugs on neurons and oligodendrocytes have often been attributed to indirect effects caused by the actions of MS drugs on peripheral immune cells (e.g., [28]). Therefore, the effects of MS drugs have not been documented in multiple CNS cell types nor integrated into a common molecular cascade of events. The goal of the present review is to describe and compare the molecular effects of the traditional and recent FDA-approved MS drugs on multiple CNS cell types, focusing on microglia within the generally applied homeostatic (M0), pro-inflammatory (M1) and anti-inflammatory (M2) designation [32][33], and on astrocytes within the homeostatic (A0), reactive (A1) and neuroprotective (A2) nomenclature [34], as well as on neurons and oligodendrocytes.

2. Main Results

Except for IFN-β, the various FDA-approved MS drugs described in the review have a clear effect on the transition from a pro-inflammatory M1 into an anti-inflammatory M2 microglia phenotype. This effect is particularly evident in inflammatory (EAE) as well as non-inflammatory (Cuprizone, Lysolecithin, TBI, AD) rodent models in which neurotoxicity and demyelination are central factors causing pathology. The results of the in vitro studies are in line with this inference. Moreover, most FDA-approved MS drugs reduce the inflammatory environment in the CNS by converting reactive A1 astrocytes into a neuroprotective A2 phenotype. Comparable to what holds for microglia, this effect was evident from in vitro cellular studies as well as from studies on wild-type rodents, rodent CNS-related disease models and MS patients.

Central to the mechanism of action of the FDA-approved MS drugs appeared to be NFκB signaling. NFκB is the major signal transducer involved in the activation of microglia and astrocytes towards a pro-inflammatory M1 and reactive A1 phenotype, respectively [35]. This transcription factor complex, that binds to nuclear DNA elements, is responsible for activating the transcription of a wide range of pro-inflammatory cytokines, chemokines and matrix metalloproteinases, and induces oxidative stress and inflammasome activation [36] [37]. Moreover, NFκB interacts and cooperates with two other nuclear signal transducers, STAT1 and STAT3 [38][39][40]. A number of studies has described an increased degree of phosphorylation of NFκB, STAT1 and STAT3 under various CNS disease and injury conditions, linking their activation to the induction of a number of pathological states [41][42][43][44]. The effects of the MS drugs on pro-inflammatory as well as anti-inflammatory factors, such as chemokines, growth factors and oxidative stress inducers that are transcriptionally driven by NFκB, strongly indicate that in microglia the NFκB pathway plays a key role in the molecular actions of these drugs. Moreover, in microglia both FTY720 and DMF reduce the protein levels and activation of NFκB [45][46][47][48][49][50][51][52], and virtually all MS drugs modulate the expression of a remarkable number of molecular effectors upstream of NFκB, such as MAPK and PI3K/AKT [34][47][53][52][54], and other proteins known to influence NFκB signaling. Similarly, in astrocytes most MS drugs discussed here affect the expression of pro-inflammatory and anti-inflammatory factors that is dependent on NFκB-induced transcriptional programs. In addition, in astrocytes FTY720 and LQ diminish NFκB protein levels and activation [55][56][57][58][59][60][61][62][63], and nearly all of the MS drugs modulate the expression of MAPK and ERK1/2 [64][65][66] as well as of other NFκB-interactor proteins. Together, these findings highlight the importance of the NFκB pathway for MS drug actions in microglia as well as astrocytes. A summary of these results is depicted in Figure 1. In this connection, one should realize that the effects of the monoclonal antibodies NZ, AZ and OCR on CNS cells have not yet been sufficiently studied. Furthermore, IFN-β seems to stimulate rather than inhibit the pro-inflammatory NFκB and STAT1 pathways [67][68][69][70][71], and the STAT1-related kinases JAK1 and TYK1 [70] in microglia and astrocytes [68][71][72][73].
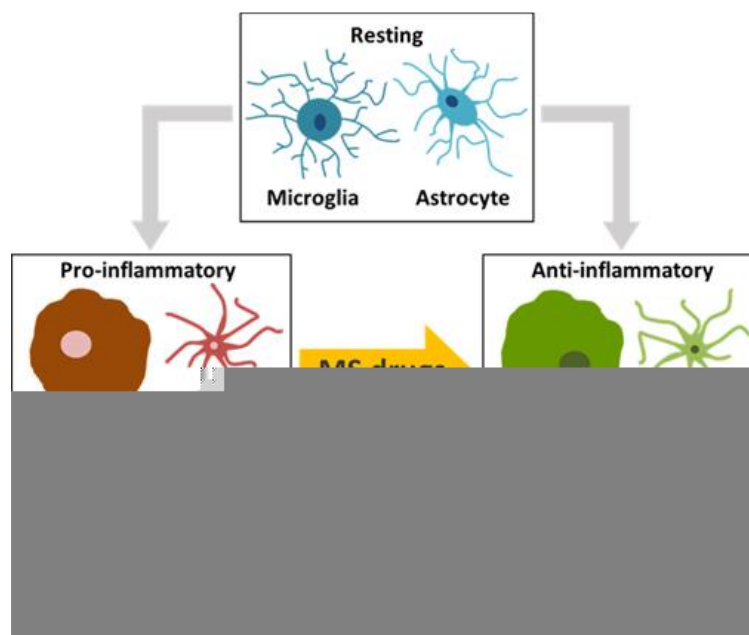

Figure 1. The effects of traditional and more recent FDA-approved MS drugs may be partially attributed to their influence on glial cells and neurons of the CNS. A common molecular effect of these drugs may involve NFκB signaling, causing a switch from pro-inflammatory microglia and astrocytes to anti-inflammatory phenotypes of these CNS cell types that recently emerged as central players in MS pathogenesis. The switch may have a beneficial effect on the functioning of diseased or injured neurons and oligodendrocytes.

3. Conclusions

We provide an overview of the molecular effects of traditional and more recently FDA-approved MS drugs on four CNS cell types. The effects of these MS drugs on the peripheral immune system and their influence on immune cell infiltration via the BBB have been documented before, and were not specifically addressed in the review. From our comprehensive analysis of MS drug effects on CNS cells, we concluded that, via NFκB signaling, the majority of these drugs attenuates the pro-inflammatory M1 microglia and reactive A1 astrocytic phenotypes. On its turn, this attenuation may positively affect the functioning of diseased or injured neurons and oligodendrocytes. Such a mechanism is likely more complicated than initially thought in that microglia have recently been shown to engage a large range of activation programs which appear to be increasingly difficult to classify as purely pro-inflammatory versus anti-inflammatory [34][74]. Future characterization of the signatures of the recently described additional microglia and astrocytic subtypes, and of the extent of their pro-inflammatory or anti-inflammatory state, will aid in obtaining an even more detailed molecular understanding of the CNS mechanisms of action of drugs targeting MS. Knowledge of these molecular mechanisms may help anticipating adverse drug effects and in considering the use of combinatorial drug therapy to treat this complex neuroinflammatory disease.

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