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Review

Female sex steroids and glia cells: Impact on multiple sclerosis lesion formation and fine tuning of the local neurodegenerative cellular network

Markus Kipp[a,*], Tanja Hochstrasser[a], Christoph Schmitz[a], Cordian Beyer[b]

[a] Department of Neuroanatomy, Ludwig-Maximilians-University of Munich, Munich, Germany
[b] Institute of Neuroanatomy, Faculty of Medicine, RWTH Aachen University, 52074 Aachen, Germany

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ABSTRACT

Multiple sclerosis (MS) is a chronic inflammatory and demyelinating disease that shows a female-to-male gender prevalence and alleviation of disease activity during late stage pregnancy. In MS-related animal models, sex steroids ameliorate symptoms and protect from demyelination and neuronal damage. Underlying mechanisms of these protective avenues are continuously discovered, in part by using novel transgenic animal models. In this review article, we highlight the regulation of glia cell function by female sex steroids. We specifically focus on the relevance of glia cells for immune cell recruitment into the central nervous system and show how estrogen and progesterone can modulate these cell-cell communication pathways. Since MS is considered to have a strong neurodegenerative component, principal neuroprotective mechanisms, exerted by sex-steroids will be discussed as well. Activation of steroid receptors might not just act as immunosuppressant but at the same time harmonize brain-intrinsic networks to dampen neurodegeneration and, thus, disease progression in MS.

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Abbreviations: AD, Alzheimer's disease; ADIOL, 5-androsten-3ß, 17ß-diol; AIDT, autoimmune thyroid disease; Akt, Serine/threonine kinase; ALS, amyotrophic lateral sclerosis; ATP, adenosine tri-phosphate; BBB, blood–brain barrier; BDNF, brain-derived neurotrophic factor; CCL, chemokine (C-C motif) ligand; CD, cluster of designation; CIS, clinically isolated syndrome; CNS, central nervous system; CNP, 2′,3′-cyclic nucleotide 3′-phosphodiesterase; CtBP, C-terminal-binding protein 1; DAMPs, damage-associated molecular pattern; 25-Dx, putative membrane progesterone receptor; E2, 17ß-estradiol; EAE, experimental autoimmune encephalomyelitis; ER, estrogen receptor; ERK1/2, extracellular signal-regulated kinases 1/2; FGF, fibroblast growth factor; GD, Graves' disease; GDNF, glial-derived neurotrophic factor; GFAP, glial fibrillary acidic protein; GPR30, G protein-coupled estrogen receptor 30; HT, Hashimoto's thyroiditis; IBA1, ionized calcium-binding adapter molecule 1; IFNγ, interferon gamma; IGF1, insulin-like growth factor 1; IL, interleukin; LPS, lipopolysaccharides; MBP, myelin basic protein; MCP, monocyte chemoattractant protein; MCT, monocarboxylate transporter; MHC, major histocompatibility complex; MMP, matrix metalloproteinase; mPRα, membrane progesterone receptor alpha; MHV, mouse hepatitis virus; MS, multiple sclerosis; mTOR, mechanistic target of rapamycin; Necl-1, nectin-like 1; NLRP, NOD-like receptor protein; NO, nitric oxide; Nrf2, nuclear factor (erythroid-derived 2)-like 2; Olig2, oligodendrocyte transcription factor 2; OPC, oligodendrocyte precursor cell; P, progesterone; PAMPs, pathogen-associated molecular pattern; PD, Parkinson's disease; PDGFRα, platelet-derived growth factor receptor alpha; Pgrmc1, progesterone receptor membrane component 1; PI3K, phosphoinositide-3-kinase; PLP, proteolipid protein; PPMS, primary progressive MS; PR, progesterone receptor; RA, rheumatoid arthritis; ROS, reactive oxygen species; RRMS, Relapsing remitting MS; SLE, systemic lupus erythematosus; SPMS, Secondary progressive MS; SFV, Semliki Forest virus; TBI, traumatic brain injury; TGFß, transforming growth factor-beta; Th cell, T helper cell; TLR, Toll-like receptors; TMEV, Theiler's murine encephalomyelitis virus; tMCAO, transient focal middle cerebral artery occlusion; TNFα, tumor necrosis factor alpha; VCAM-1, vascular cell adhesion molecule 1; VLA-4, integrin alpha4beta1 (very late antigen-4).

* Corresponding author.
E-mail address: markus.kipp@med.uni-muenchen.de (M. Kipp).

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1. Multiple sclerosis: General remarks

Multiple sclerosis (MS) is a complex, multifactorial, polygenic disease, influenced by various factors including age, gender, hormones and environmental impacts. The most widely accepted hypothesis is that auto-reactive T and B cells induce myelin damage, neuroinflammation and neurodegeneration (Bedoya et al., 2013). Additionally, primary oligodendrocyte dysfunction has been considered as a potential disease-promoting or -triggering factor (Barnett and Prineas, 2004). For example, a particular subtype of active MS lesions, so called pattern III according to the classification of Lucchinetti et al. (2004), are characterized by the selective early loss of myelin-associated glycoprotein and cyclic nucleotide phosphodiesterase (both proteins are exclusively synthesized by oligodendrocytes in the brain) together with apoptotic cell death of oligodendrocytes. It was shown in independent studies that active MS lesion development, if investigated at an early stage, may be characterized by oligodendrocyte stress, focal microglia activation but little T-cell recruitment (Barnett and Prineas, 2004; De Groot et al., 2001). This led to the assumption that neurodegenerative events play an important role during early MS lesion formation. Whatever the trigger factors for lesion formation in MS are, we now know that central and peripheral cellular and immune-related components are critically involved in lesion development and progression.

Despite being of unknown etiology, the histopathological hallmarks of MS lesions are quite well-defined. They include focal as well as diffuse demyelination, oligodendrocyte loss and activation of brain resident inflammatory cells such as microglia and astrocytes. Furthermore, damage of the neuro-axonal unit is pivotal for disease progression. Such cellular alterations can be found in various regions of the central nervous system (CNS) including diverse white and gray matter areas (Kipp et al., 2012a; Bo et al., 2006). MS affects patients of all ages, but symptoms are most likely to appear first in individuals between 20 and 50 years of age.

The diagnosis "*Multiple sclerosis*" requires evidence of lesions in at least two separate areas of the CNS, including brain, spinal cord and optic nerves (dissemination in space), and evidence that new lesions developed at different time points (dissemination in time) (McDonald et al., 2001). Due to the fact that inflammatory foci can arise in virtually any CNS region, symptoms can principally be related to any CNS function, including visual disturbances, paresthesias, ataxy or muscle weaknesses. Furthermore, cognitive impairment is also a frequently observed phenomenon in MS patients, but was underestimated for a long time (Benedict and Zivadinov, 2011). MS can present in different clinical courses. A clinically isolated syndrome (CIS) is a patient's first neurological episode caused by inflammation and demyelination. The long-term risk of developing clinically definite MS after a CIS is 60 to 80% when lesions consistent with MS are seen on MRI, and about 20% when the CNS scan is normal. Relapsing remitting MS (RRMS) is the most common disease course affecting about 85% of all MS patients. RRMS means that symptoms appear (*i.e.* a relapse) and then fade away either partially or completely (*i.e.* remitting). Secondary progressive MS (SPMS) is characterized by chronically progressive clinical worsening over time. This progressive course may develop slowly after an initial CIS but usually follows a period of well-defined RRMS. During the transition from RRMS to SPMS, relapse frequency decreases but quickening of neurodegeneration can be observed. In about 15% of patients, classical relapses cannot be clearly delineated from the very beginning of the disease, despite clinical deterioration, a disease course called primary progressive MS (PPMS). A PPMS patient's rate of progression may vary over time with an occasional plateau or even temporary improvement, but the overall progression remains continuous (Lublin and Reingold, 1996).

As pointed out above, it is widely accepted that the common pathogenic pathway in MS involves the activation of the peripheral immune system finally targeting CNS myelin and neurons. Over the last three decades, major advances could be achieved in the field of MS immunotherapy. The immunotherapeutic modalities can be divided into two main groups: those affecting the acute stages (relapses) of the disease, and long-term treatments that aim at decreasing relapse frequency (*i.e.* disease modifying treatments) and progression of irreversible clinical disability. Corticosteroids are mainly used to reduce the acute inflammation that spikes during a relapse. These multimodal drugs act by inhibiting lymphocyte proliferation (Lim et al., 2007), inducing apoptosis in peripheral blood leukocytes (Leussink et al., 2001), ameliorating the synthesis of pro-inflammatory cytokines (Frankenberger et al., 2005), and reducing the expression of cell surface molecules required for immune function (Rozkova et al., 2006). Furthermore, it is believed that corticosteroids stabilize the blood-brain barrier (BBB), for example, by decreasing the expression of angiopoietin-1 and vascular endothelial growth factor-A, both well-known to regulate its permeability (Kim et al., 2008). Alternatively, plasmapheresis (*i.e.* removal of blood components) might be applied to help combat severe symptoms of relapses in patients who are not responding well to corticosteroids. In contrast, disease-modifying drugs are prescribed with the aim to reduce the relapse frequency. Currently, this group includes β-interferons (Avonex®, Betaseron®, Extavia®, and Rebif®), fingolimod (Gilenya®), glatiramer acetate (Copaxone®), mitoxantrone (Novantrone®), natalizumab (Tysabri®), alemtuzumab (Lemtrada®), teriflunomide (Aubagio®), and dimethyl fumarate (Tecfidera®).

As listed above, several approved therapies are available to decrease relapse frequency in RRMS patients. Relapses are, however, just one clinical aspect of MS. While inflammation drives the relapses, the extent of irreversible destruction of neurons (*i.e.* somata, axons and dendrites) determines accumulation of irreversible clinical disability. Our bright hope for overtly inflammatory forms of MS contrasts with ongoing challenges in progressive forms, which include PPMS and SPMS. Many therapies with efficacy in RRMS (*i.e.* reducing the relapse rate in these patients) have produced disappointing results with respect to the prevention of clinical progression, the substrate of neurodegeneration (Rice et al., 2000; Coles et al., 1999). Indeed, neuroprotection has proven to be a harder nut to crack than anti-inflammation. Novel therapeutic strategies that specifically target the neurodegenerative aspect of MS include blockade of Na^+ voltage-gated Ca^{2+} channels, Lingo-1 antagonism which is assumed to promote remyelination and axonal regeneration, erythropoietin (a hematopoietic growth factor commonly used to treat anemia), cannabis or statins (Luessi et al., 2012). Ongoing clinical studies will show the efficacy of these novel candidate