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Review

Neurophysiology of synaptic functioning in multiple sclerosis

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HIGHLIGHTS

- Excitotoxicity is emerging as a crucial determinant of early neurodegeneration in MS.
- Specific inflammatory cytokines alter glutamatergic and GABAergic transmission.
- Compensatory plasticity can influence both clinical recovery and disease progression.

ABSTRACT

Multiple sclerosis (MS) is an inflammatory immune-mediate disorder of the central nervous system (CNS), primarily affecting the myelin sheath and followed by neurodegeneration. Synaptic alterations are emerging as critical determinants of early neurodegeneration in MS.

Inflammation-induced alterations of synaptic transmission and plasticity have been investigated in vitro and also in human MS using transcranial magnetic stimulation (TMS) techniques. Specific inflammatory cytokines alter glutamatergic and GABAergic transmission, resulting in synaptic hyperexcitability. In both experimental autoimmune encephalomyelitis (EAE) and MS, excitotoxic damage and neurodegeneration are found even in the early phases of disease, conversely inflammation persists in the progressive phases.

Inflammatory cytokines also affect synaptic plasticity, as both long-term potentiation (LTP) and long-term depression (LTD) are altered in EAE and in MS patients. In particular, inflammation profoundly subverts plasticity and influence both clinical recovery after a relapse and disease course. Regulation of neuronal activity by cytokines plays important roles in the neuro-immune crosstalk involved in inflammation-associated excitotoxic neuronal damage, and in the chance of developing compensatory plasticity.

Innate and adaptive immunity interact with the CNS in MS, in line with the concept that cytokines and chemokines, in concert with neurotransmitters and neuropeptides, represent a major communication system in the CNS.

Contents

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1. Introduction

Multiple sclerosis (MS) is an inflammatory, immune-mediated disorder of the central nervous system (CNS) which is classically considered a pathology of the myelin sheath followed by late brain and spinal atrophy. Independently of white matter pathology, synaptic alterations and in particular excitotoxic damage are emerging as critical determinants of early neurodegeneration in MS. In line with the excitotoxic hypothesis, in animal models of MS (experimental autoimmune encephalomyelitis, EAE), both enhanced glutamatergic signaling and reduced GABAergic transmission have been described (Castegna et al., 2011; Clements et al., 2008; Centonze et al., 2009; Gottesfeld et al., 1976; Kan et al., 2014; Pitt et al., 2000; Sarchielli et al., 2003; Rossi et al., 2011b; Werner et al., 2001). In addition, altered levels of both glutamate and GABA have been reported in the cerebro-spinal fluid (CSF) (Sarchielli et al., 2003; Stover et al., 1997) and in the brain of MS patients (Cawley et al., 2015; Srinivasan et al., 2005). Furthermore, both in EAE and MS altered glutamate clearance and receptor expression have been found (Hardin-Pouzet et al., 1997; Pitt et al., 2000; Smith et al., 2000; Ohgoh et al., 2002; Geurts et al., 2003, 2005; Vallejo-Illarramendi et al., 2006). Accordingly, oligodendrocyte and neuronal damage is partly prevented by the administration of glutamate receptor antagonists (Bolton and Paul, 1997; Centonze et al., 2009; Pitt et al., 2000; Smith et al., 2000; Wallström et al., 1996; Plaut, 1987). Overall, the excitotoxic hypotheses contribute to add novelty on both the pathogenesis and prognosis of MS.

In the first and in the second part of this review article, we will summarize the experimental studies showing that in EAE and MS specific proinflammatory cytokines induce alterations of both glutamatergic and GABAergic transmission, resulting in synaptic hyperexcitability. Proinflammatory cytokines, such as interleukin-1β (IL-1β) and tumor necrosis factor α (TNFα), are soluble mediators released by immune cells, able to activate inflammatory response. We will also overview the clinical studies in MS patients using transcranial magnetic stimulation (TMS), showing alterations of both excitatory and inhibitory intracortical circuits in relation to different phenotypes and disease phases.

In the third part, we will discuss studies exploring neural plasticity either in vitro or in MS patients, using TMS. Brain plasticity and its influence on clinical expression have been explored in experimental models of MS. In EAE mice, inflammatory lesions of the corticospinal tract (CST) induce anatomical changes in the connections of the spared neighboring interneurons and in the projections of unlesioned CST fibers, leading to a functional remodeling of motor cortex which is important for clinical recovery (Kerschensteiner et al., 2004). Morphological changes of spinal motoneuron synapses have also been investigated in EAE during exacerbation and after remission. In particular, both synaptic retraction during disease exacerbation and recovery of presynaptic contacts during remission phase have been reported (Marques et al., 2006). Also in MS patients, both cortical synaptic loss and increased synaptogenesis compared to controls have been described (Wegner et al., 2006; Schirmer et al., 2013). In this part, we will focus on TMS studies performed in MS patients, which highlighted that specific plasticity alterations are associated with different disease phenotypes (relapsing-remitting, RR-MS; primary progressive, PP-MS), or phase (remitting, relapsing), and that a specific subset of inflammatory cytokines is responsible for these alterations. In this scenario, long-term potentiation (LTP) seems to be able to minimize neuronal damage, bringing back the excitability of those neurons which have partly lost synaptic inputs. These phenomena seem to modulate the clinical expression of disease and disability progression. Moreover, the concept of plasticity reserve is emerging as a new marker to predict clinical recovery.

In the last part, we will examine the role of different proinflammatory and anti-inflammatory cytokines, together with neurotrophic factors, on synaptic function and disease manifestations. It has been demonstrated that cytokines can influence both neuronal survival and clinical manifestation by modulating synaptic transmission (Centonze et al., 2009; Rossi et al., 2011a). Overall, these data are in line with the hypothesis that cytokines and chemokines, together with neurotransmitters and neuropeptides, represent a major communication system in the CNS.

2. Inflammation and synaptic transmission in EAE

2.1. Glutamatergic transmission

In a previous study (Centonze et al., 2009), we have first investigated the effects of inflammation on synaptic transmission in the striatum of EAE mice. We found that aberrant excitatory transmission was associated with altered function of the main ionotropic glutamate receptor, termed α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor channel complex (Fig. 1). These alterations occurred even before the clinical manifestations and were associated to neurodegeneration, supporting the notion that in MS the neuronal compartment and the white matter are involved together, although independently (Centonze et al., 2009). It has been previously suggested that AMPA receptors are involved in the neurodegeneration of EAE (Kanwar et al., 2004), this was further confirmed by the evidence that administration of 2,3-dihydroxy-6-nitro-7-sulfamoyl-benzoquinoxaline-2,3-dione