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Review

# Acquired channelopathies as contributors to development and progression of multiple sclerosis

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ABSTRACT

Multiple sclerosis (MS), the most frequent inflammatory disease of the central nervous system (CNS), affects about two and a half million individuals worldwide and causes major burdens to the patients, which develop the disease usually at the age of 20 to 40. MS is likely referable to a breakdown of immune cell tolerance to CNS self-antigens resulting in focal immune cell infiltration, activation of microglia and astrocytes, demyelination and axonal and neuronal loss. Here we discuss how altered expression patterns and dysregulated functions of ion channels contribute on a molecular level to nearly all pathophysiological steps of the disease. In particular the detrimental redistribution of ion channels along axons, as well as neuronal excitotoxicity with regard to imbalanced glutamate homeostasis during chronic CNS inflammation will be discussed in detail. Together, we describe which ion channels in the immune and nervous system commend as attractive future drugable targets in MS treatment.



**Contents**



## Introduction

In MS auto-aggressive immune cells cross the blood–brain barrier, enter the CNS of genetic susceptible individuals and set up an inflammatory environment leading to demyelination and axonal and neuronal degeneration, which in turn is the cause of the irreversible and progressive disability of MS patients (Compston and Coles, 2008). However, the underlying mechanisms and molecular pathways of immune cell tolerance breakdown and neuro-axonal injury are still enigmatic. Indeed, understanding these processes in detail would be fundamental, since no cure is available and current therapies primarily target the relapse rate of the patients, which at best correlates moderately with disease progression (Scalfari et al., 2010).

Ion channels, pore-forming membrane spanning proteins, which control the flow of ions into or out of the cell, are important not only for the generation of membrane and action potential of excitable cells like neurons but also for the regulatory functions of nearly every cell type. Therefore ion channels, which can be among others ligand-, voltage- or second messenger-gated, are crucial for the interaction of the cell with its environment and mutations in genes that encode ion channel subunits lead to diverse neurological channelopathies ranging from epilepsy and migraine to movement disorders and psychiatric disorders (Kullmann, 2010). Furthermore, altered expression pattern or modified open probability of non-mutated ion channels can engender

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acquired channelopathies in diverse neurological diseases, among those also in MS.

Here we discuss ion channels that have recently been reported to be maldistributed, dysfunctional or pathologically activated in immune and CNS-resident cells in MS and its animal model experimental autoimmune encephalomyelitis (EAE) (Table 1). Thereby ion channels likely contribute to aberrant immune cell activation and polarisation as well as neuro-axonal degeneration during chronic CNS inflammation. This idea is supported by a great variety of ion channel blockers that have shown disease-modulating capacities in the EAE model. This commends ion channels as attractive drugable targets in MS, with ligand-gated and voltage-gated channels already being placed in the top five gene families that are targeted by currently available drugs in other indications (Overington et al., 2006).

## Dendritic cells

By orchestrating adaptive immunity, dendritic cells represent key antigen-presenting cells (APCs) that initiate and modulate immune responses. Importantly, the nature of a dendritic cell's interaction with a lymphocyte decides whether an effector immune response ensues or immune tolerance is established (Steinman, 2012). Hence, understanding the influence of ion channels expressed by dendritic cells on the

**Table 1**
Acquired channelopathies in multiple sclerosis.

| Ion channels or related molecules | Alternations in CNS inflammation and potential effects on disease development and progression |
|---|---|
| *Dendritic cells* | |
| $K_v1.3$ and $K_v1.5$ | Highly expressed on brain infiltrating dendritic cells in MS lesions and probably involved in regulation of dendritic cell maturation and cytokine release (Mullen et al., 2006) |
| mGluR4 | *mGluR4*$^{-/-}$ mice show exacerbated EAE, because signalling through mGluR4 on dendritic cells lead to development of regulatory T cell (Fallarino et al., 2010) |
| *T cells* | |
| STIM1 | Mice lacking the CRAC channel activator STIM1 on T cells are resistant to EAE induction due to loss of antigen-specific T cell responses (Ma et al., 2010; Schuhmann et al., 2010) |
| $K_v1.3$ | Highly expressed on $T_{EM}$ in MS brains; inhibition or genetic deficiency of $K_v1.3$ in T cells ameliorates EAE course (Beeton et al., 2001; Gocke et al., 2012; Rus et al., 2005; Wulff et al., 2003) |
| TASK1 | *Task1*$^{-/-}$ mice show reduced clinical scores during EAE with decreased numbers of CNS-infiltrating T cells (Bittner et al., 2009; Meuth et al., 2008a) |
| TASK2 | Increased TASK2 expression on T cells in MS patients; inhibition of TASK channels reduces secretion of pro-inflammatory cytokines and T cell proliferation (Bittner et al., 2010) |
| *Blood–brain barrier* | |
| TREK1 | Reduced endothelial expression in MS lesions; *Trek1*$^{-/-}$ mice show exacerbated EAE probably due to increased immune cell trafficking into the CNS (Bittner et al., 2013) |
| TRPV1 | SNPs in the *TRPV1* gene correlate with MS disease severity; *Trpv1*$^{-/-}$ mice show ameliorated EAE due to reduced blood–brain barrier permeability (Paltser et al., 2013) |
| *Astrocytes* | |
| $Na_v1.5$ | $Na_v1.5$ is up-regulated on astrocytes in MS lesions (Black et al., 2010) |
| P2X7 | Increased expression of P2X7 on reactive astrocytes around MS lesions and after IL-1β stimulation in vitro; up-regulation will lead to higher calcium influx and increased NOS production (Narcisse et al., 2005) |
| *Microglia* | |
| $Na_v1.6$ | Only activated microglia in EAE and MS show high $Na_v1.6$ expression; loss of channel function results in reduced CNS infiltration in EAE and decreased phagocytic function of activated microglia in vitro (Craner et al., 2004a) |
| N-type $Ca^{2+}$ $\alpha_{1B}$ subunit | Microglia cells of mice that lack this subunit produce decreased amounts of CCL2 resulting in reduced immune cell infiltrate and ameliorated EAE; treatment of EAE with a specific N-type VGCC blocker reduces microglia activation and disease severity (Gadjanski et al., 2009; Tokuhara et al., 2010) |
| *Neurons* | |
| $Na_v1.2$ | Expression is distributed from the nodes of Ranvier to the demyelinated axolemma in EAE mice and MS lesions (Craner, 2004; Craner et al., 2004b); sodium channel blocker displays neuro-protective effects in EAE (Bechtold et al., 2004, 2006; Black et al., 2007; Morsali et al., 2013) |
| $Na_v1.6$ | In addition to $Na_v1.2$ like distribution, $Na_v1.6$ occurs mainly in injured and dying neurons; EAE severity is reduced in *Scn2b*-deficient mice which also show less axonal loss (Craner, 2004; Craner et al., 2004b; O'Malley et al., 2009) |
| $Na_v1.8$ | Under physiological conditions $Na_v1.8$ is only expressed in the PNS, but the channel is highly up-regulated in cerebellar Purkinje cells in EAE and MS; genetic deficiency or pharmacological blockade attenuates EAE severity; might contribute to cerebellar dysfunction of MS patients (Black et al., 2000; Damarjian et al., 2004; Saab et al., 2004; Shields et al., 2012) |
| $K_v1.1$, $K_v1.2$ and $K_v2.1$ | $K_v1.1$ and $K_v1.2$ are normally expressed at the juxtaparanodal membrane but $K_v1.2$ is distributed over the entire demyelinated axon in EAE; blockade of $K_v1.1$ ameliorates the EAE course; $K_v2.1$ is down-regulated in the spinal cord of EAE mice (Beraud et al., 2006; Jukkola et al., 2012) |
| ASIC1 | Expressed within the somata and dendrites of neurons in healthy CNS tissue—during acute EAE as well as in MS lesions ASIC1 is also expressed in injured axons and oligodendrocytes; *Asic1*$^{-/-}$ mice and inhibition ameliorate EAE course (Friese et al., 2007; Vergo et al., 2011) |
| TRPM4 | In EAE and MS lesions TRPM4 spreads from the soma to the axon and co-localises with axonal injury markers; *Trpm4*$^{-/-}$ or blockade results in ameliorated EAE and axonal protection (Schattling et al., 2012) |
| VGCC | Expression of the $\alpha_{1B}$ subunit of N-type VGCC is restricted to synapse-forming nerve terminals, but chronic CNS inflammation in MS initiates also axonal expression in injured neurons; L-type and N-type VGCC seem to contribute to neuronal injury under inflammatory conditions since their pharmacological inhibition ameliorates EAE (Brand-Schieber and Werner, 2004; Gadjanski et al., 2009; Kornek et al., 2001; Ouardouz et al., 2003) |
| TASK1 and 3 | Up-regulated in EAE optic nerves and down-regulated in the thalamus and spinal cord of EAE mice and in human MS plaques (Meuth et al., 2008b) |
| Ionotropic glutamate receptors | Expression of several glutamate receptor subunits such as GluR1, 2 and 3 is up-regulated on injured axons only in active MS plaques (Newcombe et al., 2008); the GRIN2A gene which encodes the NR2A subunit of NMDAR is associated with MS disease severity (Baranzini et al., 2008; International Multiple Sclerosis Genetics Consortium, 2011); pharmacological inhibition of glutamate receptor coupled ion channels mediates neuroprotective effects in EAE (Basso et al., 2008; Centonze et al., 2009; Kanwar et al., 2004; Paul and Bolton, 2002; Pitt et al., 2000; Smith et al., 1999; Wallström et al., 1996) |
| PMCA2 | Reduced expression of the ion pump which removes calcium from the cell is reported in EAE and MS lesions (Kurnellas et al., 2005, 2010; Lock et al., 2002; Nicot et al., 2003) |

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