FEBS Letters 585 (2011) 3836–3842

journal homepage: www.FEBSLetters.org

Review

Ion channels in autoimmune neurodegeneration

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ARTICLE INFO

Article history:
Received 28 February 2011
Revised 26 March 2011
Accepted 28 March 2011
Available online 14 April 2011

Edited by Richard Williams, Alexander Fliigel and Wilhelm Just

Keywords:
Multiple sclerosis
Experimental autoimmune encephalomyelitis
Ion channel
Immune system
Neuroprotection

ABSTRACT

Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system characterized by widespread inflammation, focal demyelination and a variable degree of axonal and neuronal loss. Ionic conductances regulate T cell activation as well as neuronal function and thus have been found to play a crucial role in MS pathogenesis. Since present therapeutical approaches are only partially effective so far, ion channel modulation as a future strategy was brought into focus. Here, we review the status quo concerning recent findings from ion channel research in MS and its animal model, experimental autoimmune encephalomyelitis.

1. Introduction

Multiple sclerosis (MS) is a neuroinflammatory disease associated with demyelination and neuronal cell death. As MS is the major cause of neurological disability in young adults, many costs and research efforts have been spent to identify potential therapeutic targets. However, MS therapy is only partially effective so far. Available drugs serve to suppress and modulate the immune response, but their impact on disease progression and permanent disability is only modest [1]. Accumulating neurological deficits are due to axonal and neuronal degeneration during the disease course. Several causes are under discussion: (1) during phases of acute inflammation, neuronal and axonal damage are caused by infiltrating immune cells that induce either direct cell–cell-interactions or transmitter release (NO, glutamate); (2) damaged oligodendrocytes lead to demyelination which in turn causes an insufficient trophic supply that finally results in axonal degeneration; (3) demyelination induces alterations in distribution and expression of different ion channels and transporters in axonal membranes. Accordingly, increased electrical activity as well as augmented intracellular Ca^{2+} levels result in a dysfunction of mitochondria and neuronal cell death in the end. Thus, it seems reasonable to ask: Does MS belong to the group of channelopathies? Originally, MS was conceived as a chronic inflammatory autoimmune disease of the central nervous system which is accompanied by demyelination that either delays or blocks electrical impulse conductance in central neurons. However, the characteristic accumulation of neurological deficits during MS disease course cannot solely be explained by de- and remyelination processes. Currently, it is considered to be due to axonal and neuronal degeneration. In this context, it can be assumed that one leading mechanism is the reorganization and altered gene expression of different ion channels which occurs in demyelinated axons. Therefore, MS may be defined as a member of the group of channelopathies, i.e., disorders in which abnormal ion channel function leads to the appearance of clinical signs and symptoms. These diseases can be further subdivided in genetic, autoimmune and transcriptional/translational channelopathies. (1) Genetic channelopathies are characterized by altered ion channel structures and function that are due to mutations in the channel genes [2]. (2) The autoimmune channelopathies are a group of neurological disorders in which the patient develops raised serum levels of highly specific autoantibodies to various neuronal or muscle ligand-gated or voltage-gated ion channels, or to related functional proteins [3]. (3) The third group is comprised of translational/transcriptional channelopathies which are disorders that are caused by a dysregulated production of normal channel proteins as a result of changes in the complex and highly dynamic process of gene transcription [4]. As a consequence, neuronal cell functions are perturbed. In terms of MS

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0014-5793/$36.00
doi:10.1016/j.febslet.2011.03.065

and its animal model experimental autoimmune encephalomyelitis (EAE), a number of different reports reveal their affiliation to the third subgroup of translational channelopathies in which it is shown that the pharmacological modulation of ion channel functions ameliorates disease course and clinical severity.

Studies on EAE revealed ion channels as being key players in pathophysiological processes of MS. Ion channels on neurons but also on immune cells strongly influence basic cellular parameters like the membrane potential and calcium signaling, and hence they regulate cell activity. According to their ubiquitous expression pattern, ion channels have the potential to influence nearly every stage of MS pathogenesis. The regulation of the immune response is fundamentally dependent on ion channels which are expressed on immune cells and which allow peripheral T lymphocytes to proliferate and to produce inflammatory cytokines [5]. Ion channels on neurons and glia cells affect the mechanisms that induce axonal and neuronal degeneration in white matter of the brain and spinal cord [6,7]. The application of different sodium, potassium and calcium channel inhibitors considerably ameliorates the EAE disease course as well as clinical severity, and it postpones the disease onset after immunization in comparison to sham-treated control animals [5,8,9]. Based on these results, ion channels seem to be promising in terms of therapeutic target structures. Nevertheless, the beneficial effect in these pre-clinical blocker studies may be mediated by two distinct pathways: either the activation/inhibition of an ion channel on nerve cells or T cells may facilitate neuronal survival or mediate an immune-modulatory effect. Thus, there is still a question to be resolved: Does a particular ion channel modulation strategy exert an immune-modulatory or a neuroprotective effect in MS?

2. Ion channels on T lymphocytes

A major contribution of human T lymphocytes to autoimmune inflammation in MS pathogenesis has already been suggested. However, the underlying pathophysiological processes are poorly understood. As basic cellular T cell functions like maintenance and modulation of the membrane potential depend on a number of different ion currents, ion channels were appraised as potential target structures for future pharmacological approaches. After antigen-specific T cell activation, a long-lasting increase in intracellular Ca^{2+} levels is needed to induce gene expression, proliferation and cytokine production. This influx of cations is outbalanced by hyperpolarizing potassium currents that preserve the driving force and a stable membrane potential. The great importance of ionic currents in regulating T cell effector functions is underlined by the fact that T cell activation leads to an upregulation of a number of different ion channel genes. After chronic stimulation, human cytotoxic $CD8^+$ T cells showed a close to 10-fold upregulation of mRNA coding for a member of the two-pore domain K^+ channel (K_{2P}) family [10].

2.1. K^+ channels

By now, a number of different ion channels on T cells are identified. There are three most prominent potassium channels: a voltage-gated K^+ channel [$K_V1.3$] [11,12], a Ca^{2+}-activated and intermediate conductance K^+ channel [$K_{Ca}3.1$ or IK_{Ca}] [13,14] as well as four distinct members of the two-pore K^+ channel family: TASK1, TASK2, TASK3 and TRESK [5,10,15,16]. In T cells under basal conditions, the resting membrane potential is maintained at about −50 mV by a K^+ outward current carried by $K_v1.3$ channels. There are numerous studies showing that inhibition of $K_v1.3$ offers a promising approach to modulate pathological immune responses mediated by autoreactive effector memory T cells (T_{EM}). Selective $K_V1.3$ inhibitors do not prevent immunological synapse formation, but they suppress Ca^{2+} signaling, cytokine production and proliferation of autoantigen-specific T_{EM} at pharmacologically relevant concentrations while sparing other classes of T cells [17,18]. Although there was an apparent lack of immune system defects due to counterbalancing chloride currents in $K_V1.3$ knockout mice [19], selective blockade of $K_V1.3$ channels in miniature swines reduced the immune response in vivo [20]. $K_v1.3$ expression was found to be high in T cell clones of the appropriate antigen specificity of MS patients [21]. In addition, $K_v1.3$ positive cells were highly evident in the immune infiltrates of the majority of MS plaques [22].

A second type of K^+ current in T cells is carried by Ca^{2+}-activated and intermediate conductance K^+ channels ($K_{Ca}3.1$). Based on their K^+ conductance in the range of 20–40 pS, they can be distinguished from the closely related small ($K_{Ca}2.x$; 5–20 pS) and large conductance ($K_{Ca}1.1$; 200–250 pS) K^+ channels [23]. $K_{Ca}3.1$ channels are closed under resting conditions with low basal cytosolic Ca^{2+} levels and open rapidly if Ca^{2+} rises intracellularly. Thus, these channels support the maintenance of the membrane potential that allows the long-lasting Ca^{2+} influx after T cell receptor stimulation. Blocker studies with a highly specific blocker of these K^+ channels (TRAM-34) showed that $K_{Ca}3.1$ channels play a critical role in the immune response during the development of MOG-induced EAE in C57BL/6 mice. However, the effect of TRAM-34 application was reversible, as indicated by the development of clinical EAE symptoms within 48 h after withdrawal of treatment [9]. Additionally, the efficacy of K^+ channel blockers was assessed in rats by transferring donor lymphocytes from rats with EAE to healthy, untreated recipients [adoptive transfer (AT)-EAE] [25]. Specific and simultaneous inhibition of $K_v1.3$ and $K_{Ca}3.1$ channels by a $K_v1.3$ blocker (ShK) or by a combination of a highly specific Shk analogue (ShK-Dap22) plus TRAM-34 prevented lethal AT-EAE. Blockade of $K_v1.3$ alone with ShK-Dap22, but not of $K_{Ca}3.1$ with TRAM-34, was also effective. When administered after the onset of symptoms, ShK or the combination of ShK-Dap22 plus TRAM-34 greatly ameliorated the clinical course of both moderate and severe AT-EAE [24].

In human and murine T lymphocytes, three distinct members of the two-pore potassium channel family are constitutively expressed: TASK1, TASK2 and TASK3. In addition, the expression of the calcineurin-regulated K_{2P} channel TRESK was postulated in leukemic Jurkat T cells [16]. The functional role of TRESK in primary T cells still needs to be confirmed. However, pharmacological inhibition of TASK1, TASK2 or TASK3 leads to a reduction in cytokine production and proliferation after T cell receptor stimulation. In vivo relevance of T cells can be tested by AT-EAE. Pharmacological blockade of TASK channels on myelin basic protein (MBP)-specific T cells before transfer resulted in a significant amelioration of the disease course [15]. After induction of myelin oligodendrocyte glycoprotein (MOG)-EAE, TASK1 knockout mice showed a significantly reduced clinical severity and markedly reduced axonal degeneration compared to control animals. Stimulated T cells from TASK1 knockout animals showed impaired cell proliferation and cytokine production, while the immune repertoire and naïve T cells were otherwise normal. Supportingly, pharmacological inhibition by the endocannabinoid anandamide (a semi-selective inhibitor of TASK channels) reduced IFNγ secretion in stimulated T cells from wild-type but not from TASK1 knockout animals. Additionally, application of anandamide protected EAE animals from severe brain damage which was assessed by MRI [5]. Electrophysiological data revealed a significant contribution of TASK channels to the total outward current of T cells [15].

2.2. Calcium-release activated calcium channels, CRAC

The prolonged Ca^{2+} influx, which is obligatory for the induction of gene expression after antigen-specific stimulation, is mainly generated by Ca^{2+}-release activated Ca^{2+}(CRAC) channels [26,27]. In lymphocytes, CRAC channels are physiologically triggered by