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Transient Receptor Potential Ion Channels in the Etiology and Pathomechanism of Chronic Fatigue Syndrome/Myalgic Encephalomyelitis

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Abstract

Chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME) is a disabling condition of unknown cause having multi-system manifestations. Our group has investigated the potential role of transient receptor potential (TRP) ion channels in the etiology and pathomechanism of this illness. Store-operated calcium entry (SOCE) signaling is the primary intracellular calcium signaling mechanism in non-excitable cells and is associated with TRP ion channels. While the sub-family (Canonical) TRPC has been traditionally associated with this important cellular mechanism, a member of the TRPM sub-family group (Melastatin), TRPM3, has also been recently identified as participating in SOCE in white matter of the central nervous system. We have identified single nucleotide polymorphisms (SNPs) in TRP genes in natural killer (NK) cells and peripheral blood mononuclear cells (PBMCs) in CFS/ME patients. We also describe biochemical pathway changes and calcium signaling perturbations in blood cells from patients. The ubiquitous distribution of TRP ion channels and specific locations of sub-family group members such as TRPM3 suggest a contribution to systemic pathology in CFS/ME.

Keywords

Transient Receptor Potential Ion Channels/TRP, TRPM3, CFS/ME, Calcium Signaling

1. Introduction

The etiology and pathology of chronic fatigue syndrome/myalgic encephalomye-

litis (CFS/ME) have remained elusive despite many years of research. Currently, diagnosis is based on the International Case Criteria, which identifies post-exertional malaise, fatigue unrelieved by rest, headache, joint and muscle pain, memory and concentration impairment, sore throat, and lymph gland swelling as components of the illness. Additionally, CFS/ME exhibits neurological, endocrine, autonomic, metabolic, and immunological manifestations [1]. Chemical and food intolerances are notable, and patients commonly report exacerbation of symptoms with infections.

In this brief review, we discuss the role of transient receptor potential (TRP) ion channels in neurological and metabolic systems in CFS/ME patients possibly contributing to the clinical expression of the illness. The aim of this paper is to understand the potential role of TRP ion channels in the etiology and pathomechanism of CFS/ME. Future research may help identify suitable pathways amenable to pharmaco-therapeutic interventions.

2. TRP Ion Channels and Calcium Signaling

2.1. Structure and Function of TRP Ion Channels

TRP ion channels are six transmembrane domain ion channels comprised of six main groups in humans including the TRPA (ankyrin), TRPC (canonical), TRPM (melastatin), TRPML (mucolipin), TRPP (polycystin) and TRPV (vanilloid). TRP channels are mostly non-specific ion channels permitting entry of cations such as calcium (Ca^{2+}), sodium, and magnesium into cells. These channels are activated following fluctuations or deviations in the cellular environment induced by stressors that include temperature, pressure, chemicals, oxidative/reductive species, osmolarity, pH, toxins, and pathogens, which may contribute to an inflammatory response. TRPs are extensively expressed on most cells and dysregulations in TRPs have been identified in pathological conditions and as targets of novel treatments. Upon activation, TRP channels cause depolarization and hence activation of voltage-dependent ion channels, thus permitting changes in intracellular Ca^{2+} concentration [2].

2.2. Role in Calcium Signaling

Ca^{2+} plays an important role in intracellular signaling pathways, cell differentiation and division, apoptosis, and transcriptional events in all cells [3]. In non-excitable cells, such as immune cells, the main form of Ca^{2+} entry is known as store-operated Ca^{2+} entry (SOCE) and constitutes an essential mechanism for Ca^{2+} signaling. In brief, TRP channels are activated by various ligands binding on tyrosine kinase receptor (RTK) or G-protein-coupled receptors (GPCR), which then leads to activation of phospholipase C (PLC). PLC hydrolyzes the phosphatidylinositol 4,5-bisphosphate (PIP_2) into diacylglycerol (DAG) and inositol 1,4,5-trisphosphate (IP_3). DAG stimulates receptor-operated channels (ROC) via protein kinase C (PKC) activation [4]. ROC are mainly members of TRPC family (for example TRPC1-3-6) and contribute to the cytosolic Ca^{2+} in-

crease [5]. In parallel to PKC activation, IP_3 triggers the depletion of endoplasmic reticulum (ER) Ca^{2+} stores inducing the activation of stromal interaction molecule 1 (STIM1). STIM1 then translocates to the ER/Plasma Membrane (PM) junctions to associate and activate the PM Orai1 and/or TRP channels, mostly attributed to TRPC1. This ultimately leads to a sustained Ca^{2+} influx [6]. Hence, TRP channels and their related processes are critical in mediating Ca^{2+} signaling by monitoring intracellular Ca^{2+} stores and enabling replenishment when needed.

3. TRPM Ion Channels in Emerging Pathology

3.1. TRPM Physiology

TRP ion channel proteins, including the TRPM family, have been identified in neurodegenerative disorders indicating their substantial influence in CNS pathology [7]. In the CNS some TRP channels (e.g. TRPM2), and intracellular Ca^{2+} overload have been implicated in neuronal cell death and proinflammatory cytokine secretion [8]. Fonfria *et al.* report high TRPM3 distributions in both the brain and kidney [9]. Recent research has demonstrated that TRPM3 is highly expressed in white matter (WM) cells of the central nervous system (CNS). While the role of TRPM3 in SOCE is not well described in the literature, TRPM3 has been shown to exhibit SOCE signaling in WM cells [10].

High expression of TRPM3 in the choroid plexus within ventricles of the mouse brain is suggestive of a role in the production or ionic composition regulation of cerebrospinal fluid in the mammalian brain [11]. Given the predominant CNS distribution of TRPM3, it follows that the CNS may be a particular target for TRPM3-related Ca^{2+} dysfunction. Ca^{2+} signaling in the CNS is of fundamental importance to brain function and the integrity of the BBB [12] [13] [14]. Thiel *et al.* report other tissues that display relatively dense expression of TRPM3 include insulin-producing pancreatic β cells and eye, particularly iris and retina. Complex physiological functions affecting these cells indicate an important role for TRPM3 in physiological regulation [15]. Wagner *et al.* demonstrated that endogenous TRPM3 channels of pancreatic β cells are rapidly and reversibly activated by extracellular pregnenolone sulfate (PregS), a neuroactive steroid [16]. These authors showed that application of PregS promoted a rapid Ca^{2+} influx and subsequently enhanced insulin secretion from pancreatic islets.

Importantly, identification of an indispensable to channel function (ΔICF) deletion in TRPM3 has a major impact on TRPM3 function through impaired Ca^{2+} signaling. The ΔICF region is conserved in the TRPM family and TRPM3 variants devoid of this region are ubiquitously expressed and may constitute up to 15% of TRPM3 isoforms in different tissues. This deletion occurs in the TRPM3α7 variant, which reduces expression of normally functional variants as well as causing direct interference with their function in areas of high expression such as the CNS and pancreas. Moreover, based on observable Ca^{2+} signaling, only one TRPM3α7 protein may be expressed with up to 49 functional

TRPM3*α*2 proteins that together form 12 tetrameric channel complexes and participate in the obliteration of functional channels [17]. Variants of TRPM2 and TRPM7 have been shown to alter functional properties of these ion channels in Guamian amyotrophic lateral sclerosis and Parkinson's Disease [18] [19]. In functional studies, these authors suggest that attenuation of intracellular Ca^{2+} surges and its effect on downstream signaling pathways may contribute to the pathophysiological mechanisms in neurodegenerative diseases.

3.2. TRPM in CFS/ME

There is scant literature regarding the role of TRP channels in CFS/ME. White *et al*. found decreased TRPV1 expression to be associated with muscle pain and fatigue symptoms after exercise in MS patients and healthy controls compared with CFS/ME cases, which they attribute to adaptive down-regulation in response to enhanced receptor activation [20]. Light *et al*. reported TRPV1 expression increased significantly above baseline levels in CFS/ME patients following exercise, although the CFS/ME-control group differences remained a non-significant trend for this measure [21].

Our group has described single nucleotide polymorphisms (SNPs) in TRPM3 genes in CFS/ME, suggesting perturbations of Ca^{2+} signaling in immune cells of these patients [22] [23] [24]. We have demonstrated that dysregulation of TRP receptors, in particular, TRPM3, results in disturbed Ca^{2+} signaling and downstream kinase and gene transcription events in CFS/ME. Specifically, TRPM3 activity and natural killer (NK) cell function were impaired in CFS/ME patients. These signaling dysregulations modify Ca^{2+} concentration in the cytosol and intracellular stores, thereby altering the activation threshold of NK cells and their activity. In the study of SNPs in B cells, Marshall-Gradisnik *et al*. reported 78 SNPs were identified in nicotinic and muscarinic acetylcholine (ACh) receptor genes in CFS/ME, of which 35 were in muscarinic ACh receptor 3. We suggest these SNPs may be involved in B cell functional changes, indicating a role for Ca^{2+} dysregulation in ACh receptors and TRP ion channel signaling in the pathomechanism of CFS/ME. Arguably, the severity and nature of Ca^{2+} signaling perturbation may depend upon the isotypes and extent of TRP ion channels affected.

Interestingly, neuroimaging studies in CFS/ME patients have demonstrated changes in the brain structural connections and alterations in hemodynamic response to cognitive tasks [25] [26] [27] [28]. The consistent observations of wider regions with greater blood oxygenation level dependent activation in CFS/ME patients [29] [30] [31] could potentially be explained by disrupted neurovascular coupling, which is dependent on Ca^{2+} signaling in astrocytes [32]. Neurovascular coupling, the dynamic regulation of blood flow induced by neural activity, is a primary factor responsible for ensuring appropriate blood supply within the brain [33]. The TRPM3 family plays a key role in brain WM myelination hence dysfunction or reduced expression of the TRPM3 family identified in CFS/ME patients may impact brain functions. Both immunohistochemistry and Ca^{2+} im-

aging results indicate that TRPM3 in the CNS participates as a Ca^{2+}-permeable and sphingosine-activated channel in oligodendrocyte differentiation and CNS WM myelination [34]. Indeed, multiple and widely distributed WM abnormalities are observed in CFS/ME patients, including myelination deficits in the midbrain [25] [26], progressive WM atrophy in inferior fronto-occipital fasciculus [27], and association of disrupted sleep with WM atrophy in the medial frontal brain [28].

4. TRPM Channels as Potential Therapeutic Targets in CFS/ME

Ca^{2+} signaling pathways could be an alternative therapeutic target of TRP pathology because of their importance in various cellular processes [35]. Moreover, TRPM channels expressed at the PM could offer potential therapeutic targets and/or prognostic markers. Zierler *et al*. recently examined TRPM channels as potential therapeutic targets against pro-inflammatory diseases [36]. These authors noted that mutations in ion channels required for Ca^{2+} signaling play a role in immunodeficiencies and therefore are potential drug targets indicating the roles of TRP-Ca^{2+} pathways in inflammation. Schattling *et al*. demonstrated that TRPM4 engages in inflammation in axons in experimental autoimmune encephalomyelitis (EAE) and that the antidiabetic drug glibenclamide, which inhibits TRPM-4-like currents, resulted in reduced axonal and neuronal degeneration and attenuated clinical disease scores in EAE [37]. Research has already identified potential treatment approaches in TRP channel pathology particularly in the context of CNS neuropathies. Morelli *et al*. have reported on TRP channel pathologies, which may support drug development in these CNS conditions [38].

Importantly, TRP ion channels have a role in pain mediation and hence are targets for analgesic pharmaco-therapeutics [39]. Agonists such as the narcotic analgesic morphine operate through several opioid receptors including the μ-opioid receptor, which exerts a direct inhibitory effect on TRPM3 ion channels. Interestingly, the opioid antagonist naltrexone acts as an antagonist to the μ-opioid receptor thus negating the inhibitory function of this opioid receptor on TRPM3 without necessarily acting directly on the TRPM3 ion channel *per se* [40] [41] [42]. Although not well documented, naltrexone has been suggested in a therapeutic context in CFS/ME and the findings regarding TRPM3 may indicate a mechanism of action. Further research is indicated to establish the role of TRP channel pathology in contributing to disease and hence as potential therapeutic targets [43] [44].

5. Conclusion

CFS/ME is a complex and highly disabling condition associated with CNS and metabolic symptoms including memory and concentration impairment, widespread pain, and profound fatigue characterized by post-exertional malaise. Elucidation of these interactions has important implications for understanding pa-

thomechanisms, which are critical for characterization of this illness as well as the development of novel pharmaco-therapeutics in treatments. Reduced expression of TRP ion channels, together with their dysfunction (predominantly within the TRPM3 sub-family) has now been identified in CFS/ME patients. Further investigations, particularly regarding the TRP Ca^{2+} ion channel variants for potential pharmaco-therapeutic treatment targets, are required. Arguably, the severity and nature of Ca^{2+} signaling perturbations may depend upon the isotypes and extent of TRP ion channels affected. This may help to explain the spectrum of clinical severity of CFS/ME.

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