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Potential Therapeutic Benefit of Low Dose Naltrexone in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Role of Transient Receptor Potential Melastatin 3 Ion Channels in Pathophysiology and Treatment

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Abstract

Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) is a debilitating multi-systemic chronic condition of unknown aetiology classified as an immune dysfunction syndrome and neurological disorder. The discovery of the widely expressed Transient Receptor Potential Melastatin 3 (TRPM3) as a nociceptor channel substantially targeted by certain opioid receptors, and its implication in calcium (Ca^{2+})-dependent Natural Killer (NK) cell immune functions has raised the possibility that TRPM3 may be pharmacologically targeted to treat characteristic symptoms of ME/CFS. Naltrexone hydrochloride (NTX) acts as an antagonist to the mu (μ)-opioid receptor thus negating its inhibitory function on TRPM3. Based on the benefits reported by patients on their symptoms, low dose NTX (LDN, 3.0-5.0 mg/day) treatment seems to offer some potential benefit suggesting that its effect may be targeted towards the pathomechanism of ME/CFS. As there is no literature confirming the efficacy of LDN for ME/CFS patients *in vitro*, this study investigates the potential therapeutic effect of LDN in ME/CFS patients. TRPM3 ion channel activity was measured after modulation with Pregnenolone sulfate (PregS) and ononetin in NK cells on 9 ME/CFS patients taking LDN and 9 age- and sex-matched healthy controls using whole-cell patch-clamp technique. We report that ME/CFS patients taking LDN have restored TRPM3-like ionic currents in NK cells. Small ionic currents with a typical TRPM3-like outward rectification were measured after application of PregS, a TRPM3-agonist, in NK cells from patients taking LDN. Additionally, PregS-evoked ionic currents through TRPM3 were significantly modulated by ononetin, a TRPM3-antagonist, in NK cells from ME/CFS patients taking LDN. These data support the hypothesis that LDN may have potential as a treatment for ME/CFS by characterising the underlying regulatory mechanisms of LDN treatment involving TRPM3 and opioid receptors in NK cells. Finally, this study may serve for the repurpose of marketed drugs, as well as support the approval of prospective randomized clinical studies on the role and dose of NTX in treating ME/CFS patients.

Keywords: calcium; low dose naltrexone; myalgic encephalomyelitis/chronic fatigue syndrome; natural killer cells; opioid receptor; transient receptor potential melastatin 3; whole-cell patch clamp electrophysiology.

PubMed Disclaimer

Figures

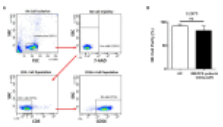

Figure 1 Natural Killer cell purity. **(A)...**

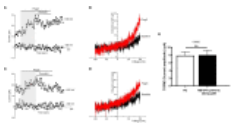

Figure 2 TRPM3 activity after PregS stimulation...

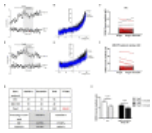

Figure 3 Modulation of PregS- evoked currents...

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