Impaired Transient Receptor Potential Melastatin 3 in Post Covid-19 Condition and Myalgic Encephalomyelitis/Chronic Fatigue Syndrome Patients

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Background

Approximately 30% of people infected by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) develop long-term effects, known as post COVID-19 condition[1,2], which is a public health concern that could be a highly prevalent long-term condition if no effective treatment becomes available[3,4]. Patients with post COVID-19 condition experience persistent and prolonged symptoms including chronic post-exertional malaise not alleviated by rest, dyspnoea, myalgia, sleep disturbances, cognitive dysfunction, and immune exhaustion[5-10]. Interestingly, symptoms observed in post COVID-19 condition resemble myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS)[6,9,11-13], which is a a multisystemic acquired condition associated with post-infectious onset, impaired natural killer (NK) cell cytotoxicity and Transient Receptor Potential Melastatin 3 (TRPM3) ion channel dysfunction[14-16].

Aim

This study aimed to characterize TRPM3 activity in post COVID-19 condition and ME/CFS patients compared with healthy controls (HC).

Methods

Whole-cell patch-clamp technique was used to measure TRPM3 ion channel activity in isolated NK cells of N=5 ME/CFS patients (fulfilling the Canadian Consensus Criteria, aged 41.0 ± 9.16, 60% female), N=5 post COVID-19 condition patients (fulfilling the World Health Organization definition, aged 50.80 ± 8.76, 60% female) and N=5 HC aged (39.8 ± 14.77, 80% female). The TRPM3 agonist, pregnenolone sulfate (PregS) was used to activate TRPM3 function, while ononetin was used as a TRPM3 antagonist. Statistical comparison was performed using the independent nonparametric Kruskal-Wallis (Dunn's multiple comparisons) test. Fisher's exact test (applying Bonferroni method) was used to determine TRPM3 sensitivity to ononetin.

Results

1- TRPM3 ion channel in HC, ME/CFS and post COVID-19 condition patients.

- **Healthy control**
- **ME/CFS**
- **Post COVID-19 condition**

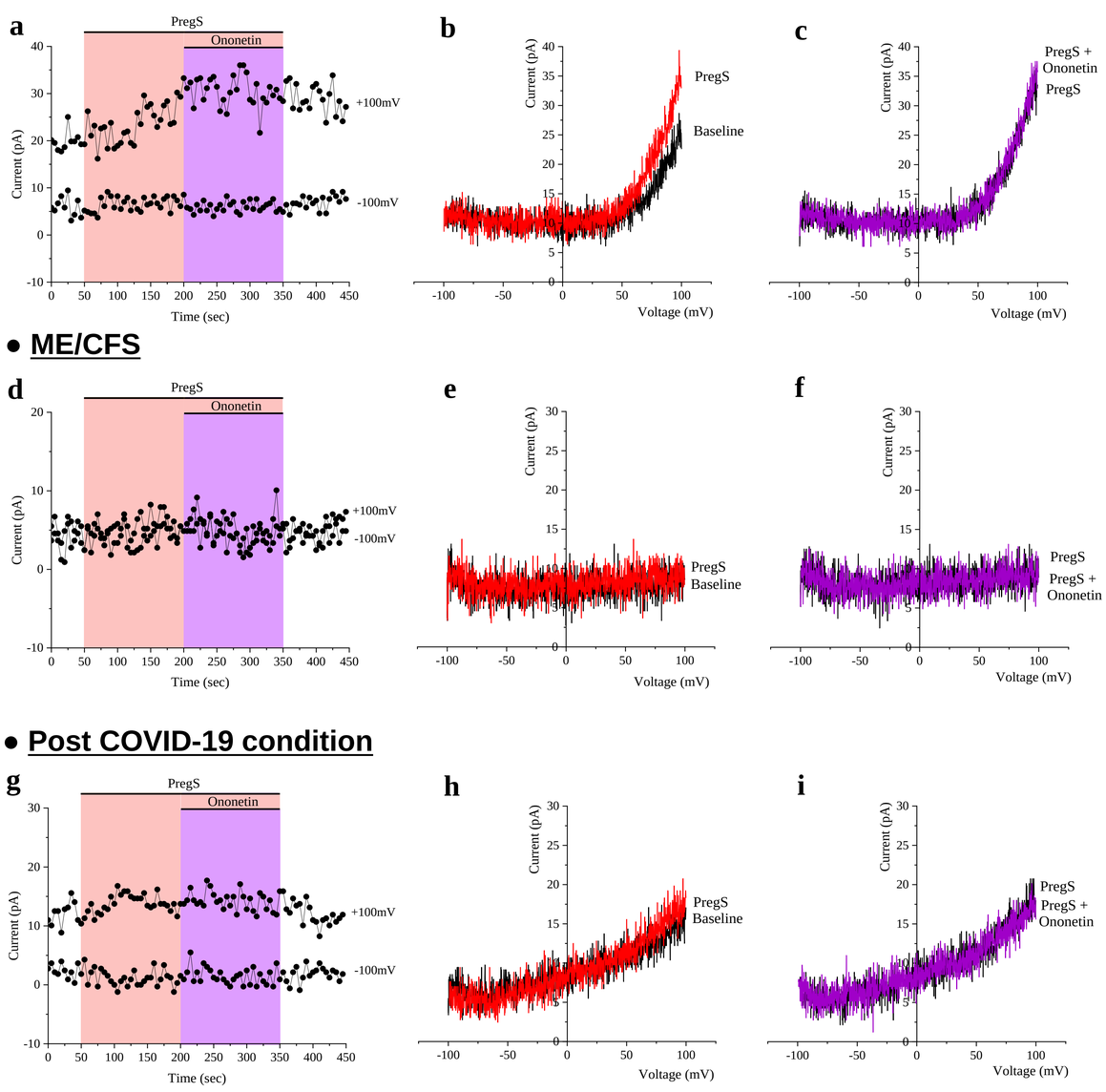


Figure 1.a.d.g. A representative time-series of current amplitude at +100mV and -100mV showing the effect of 100µM PregS and 10µM ononetin on ionic currents in isolated NK cells from HC (**a**), ME/CFS patients (**d**) and post COVID-19 condition patients (**g**). **b.e.h.** Current-voltage relationship (*I–V)* before and after PregS stimulation in a HC cell (**b**), a ME/CFS patient cell (**e**) and a post COVID-19 condition patient cell (**h**). **c.f.i.** *I–V* before and after application of ononetin in a HC cell (**c**), a ME/CFS patient cell (**f**) and a Post COVID-19 condition patient cell (**i**).

2- Impaired TRPM3 ion channel activity after PregS in ME/CFS and post COVID-19 condition patients.

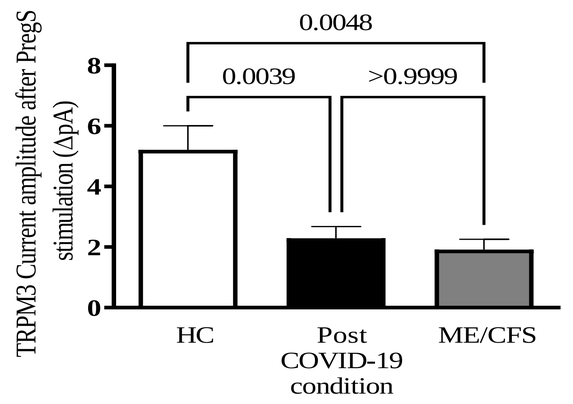
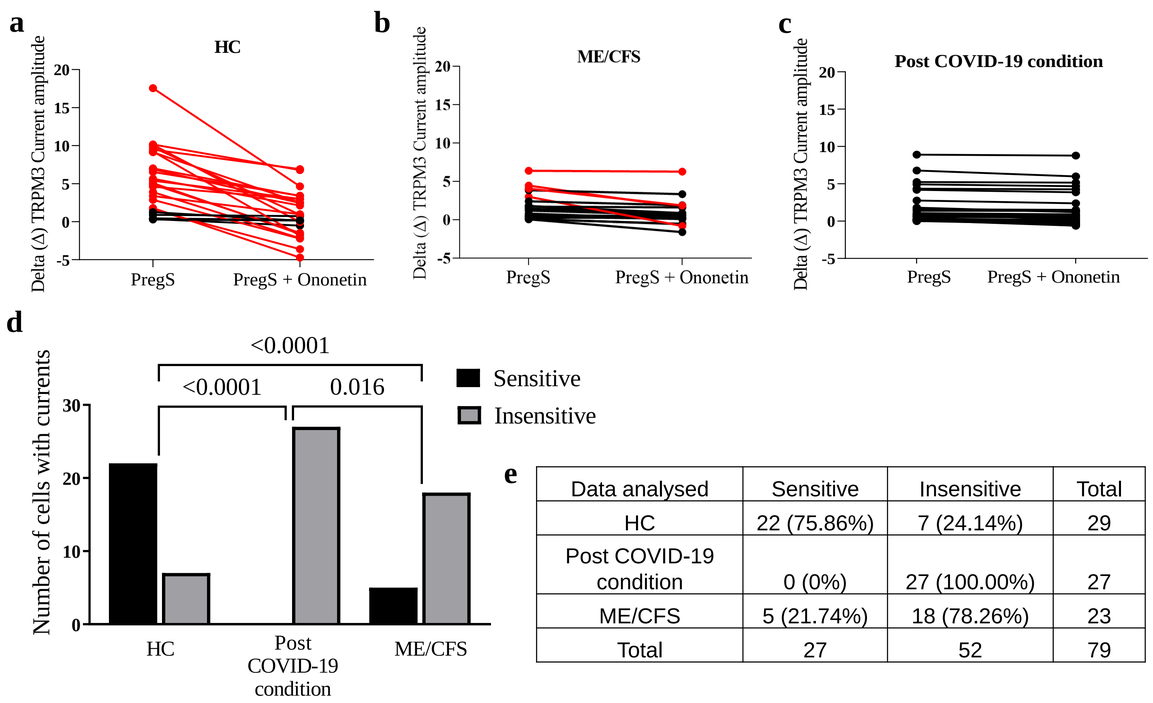


Figure 2. Bar graphs representing TRPM3 current amplitude at +100mV after stimulation with 100µM PregS in HC (N=5; n=34) compared with post COVID-19 condition patients (N=5; n=38) and ME/CFS patients (N=5; n=26). N refers to number of participants and n to number of records analysed. Data are represented as mean ± SEM.

3- PregS- evoked currents are resistant to ononetin in ME/CFS and post COVID-19 condition patients.



e

Data analysed	Sensitive	Insensitive	Total
HC	22 (75.86%)	7 (24.14%)	29
Post COVID-19 condition	0 (0%)	27 (100.00%)	27
ME/CFS	5 (21.74%)	18 (78.26%)	23
Total	27	52	79

Figure 3. Summary TRPM3 activity after ononetin modulation. **a.b.c** Scatter plots representing change of current amplitude in NK cells from HC (**a**), ME/CFS patients (**b**) and post COVID-19 condition patients (**c**) after modulation with 10µM ononetin in presence of PregS. Each cell represented as red lines indicates cells sensitive to ononetin as a reduction in amplitude was recorded. **d**. Bar graphs representing sensitive and insensitive cells to 10 µM ononetin in presence of PregS, HC patients (N=5; n=29) compared with post COVID-19 condition patients (N=5; n=27) and ME/CFS patients (N=5; n=23). Data are analysed using Fisher's exact test. **e.** Table summarizing data represented in (**d**), showing absolute number and percentage. N refers to number of participants and n to number of records analysed.

Conclusions

- **TRPM3 ion channel is impaired in NK cells from post COVID-19 condition and ME/CFS patients**.
- Provides **laboratory-based evidence** regarding the similarities between post COVID-19 condition and ME/CFS.
- TRPM3 dysfunction indicates **impaired ion mobilization** which may consequently **impede cell function**.
- **SARS-CoV-2** may be a potential infectious **trigger for ME/CFS**.
- TRPM3 dysfunction provides a **potential therapeutic target** in post COVID-19 condition.

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