Mitochondrial DNA copy number, damage, and mitochondrial respiration in Gulf War Illness

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Hypothesis: We hypothesize that mitochondrial dysfunction is an important contributor to Gulf War Illness (GWI). A corollary hypothesis is that mitochondrial parameters measured in peripheral mononuclear cells (PBMCs) can be used as a biomarker for mitochondrial dysfunction in affected tissues in GWI.
Methods: For this GWIRP New Investigator Award, we are measuring mitochondrial DNA (mtDNA) copy number and damage, as well mitochondrial respiration, in PBMCs. To date, we have analyzed samples from >100 veterans, approximately 75% of whom have GWI. We also collected detailed survey data on demographics, deployment, exposure to pesticides and pyridostigmine bromide, and current biometrics, health and activity levels.
Preliminary results: We observe a 7% increase (509 vs 474 mtDNAs/PBMC) in copy number in veterans with GWI, in keeping with prior work, when analyzing on a binary case-control basis. To date, we have not seen differences in mtDNA damage. ATP-linked oxygen consumption and, most strikingly, spare respiratory capacity were 31% and 40% respectively lower in GWI veterans, assessed on a binary basis and unadjusted for mtDNA copy number. These results suggest that less oxygen is being used to generate energy, and that mitochondria in PBMCs from veterans with GWI have less ability to ramp up activity when stressed. Spare respiratory capacity also trends down when plotted as a function of the number of symptom domains with Kansas Score of 2, rather than as a binary outcome. Our results also support previous associations of use of pyridostigmine bromide with GWI: we found an odds ratio of 3.1 ($p = 0.01$, 95% confidence interval 1.3 to 7.8), after adjusting for mtDNA copy number, using a summed Kansas score. We found an odds ratio of 3.2 of GWI ($p = 0.04$, 95% confidence interval 1.1 to 9.8), after adjusting for PB use, per 100 mtDNAs/PBMC increase.
Conclusion: Our results are consistent with decreased mitochondrial function, despite increased mitochondrial content, in PBMCs in GWI. In ongoing work, we are processing additional samples (goal of 152 individuals) and carrying out statistical analysis of additional factors that may relate to mitochondrial dysfunction. Future work should include examination of subpopulations of PBMCs.