Bioenergetics in Veterans with Gulf War Illness

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RAC-GWVI Meeting

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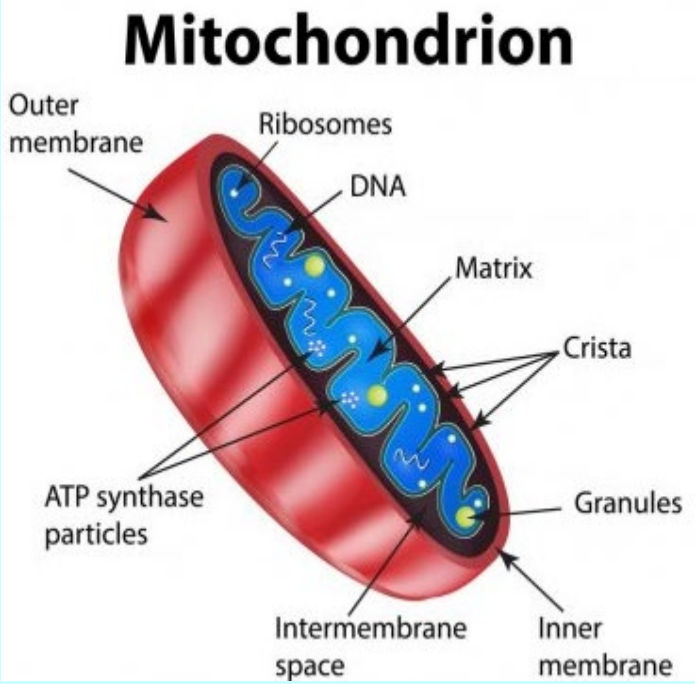
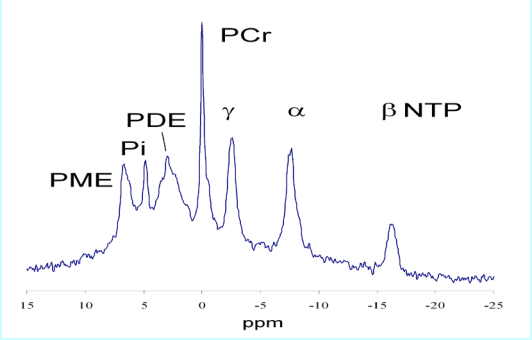
Case for Mitochondrial (mt) / Bio Energetic Involvement in GWI

- **Exposures, e.g. AChEi[1,2]**
- **Symptoms[3,4]: Multiple; focus, fatigue, muscle, brain; protean; vbl onset latency**
- **Conditions[4]: HTN, ALS, …**
- **Treatment[5]: Coenzyme Q10 (CoQ10)**
- **Mt involved in GWI + animal models data:**
  - **Animal[6-9]**
  - **Human[10,11]; Mt genetics now implicated![12]**

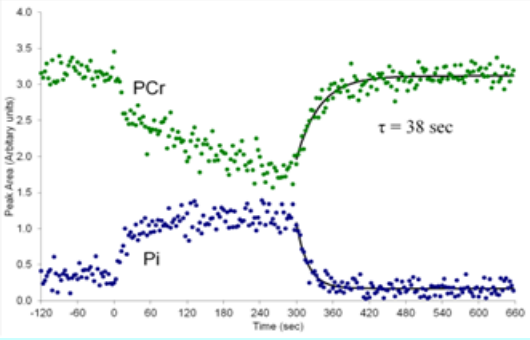


"Mitochondria structure. Vector illustration on isolated background." By Timonina. From https://www.shutterstock.com/image-vector/mitochondria-structure-vector-illustration-on-isolated-495621457

1. Golomb BA. *Proc Natl Acad Sci USA* 2008;105:4295-300. 2. Golomb, BA. *Nature Precedings.* 2012;7. 3. Fukuda K. *Jama* 1998;280:981-8. 4. Steele L. *Am J Epidemiol* 2000;152:992-1002. 5. Golomb BA. *Neural Comput* 2014;26:2594-651. 6. Zakirova Z. *Proteomics* 2017;11:1600190. 7. Shetty GA. *Front Mol Neurosci* 2017;10:182. 8. Abdullah L. *Toxicology*. 2016;372:22-33. 9. Ramirez-Sanchez I. *Sci Rep.* 2020;10(1):14526. 10. Koslik HJ. *PLoS ONE* 2014;9:e92887. 11. Chen Y. *PLoS One* 2017;12:e0184832. 12. Bui L. GWI State of the Science Conference 2020, Aug 18.



↑ PCr-R in VGWI



- **PCr-R on ^{31}P-MRS: Post exercise PCr recovery time constant relates to rate ATP production, an in-vivo marker of mt fxn.**
- **Replication sample: Case - wkness ≥ mod. Ctrl - No HA.**

Replication Sample (n=16)			
	Mean	SD	P
Control	30.3	9.2	**0.017**
Case	47.7	16.5	
Previous Finding (n=14)			
	Mean	SD	P
Control	29.0	8.7	**0.023**
Case	46.1	17.9	
Combined Sample (n=30)			
	Mean	SD	P
Control	29.7	8.7	**0.001**
Case	46.9	16.6	

- **Expansion sample: No relationship. P=0.72**

VGWI: PCr-R Tied to Weakness

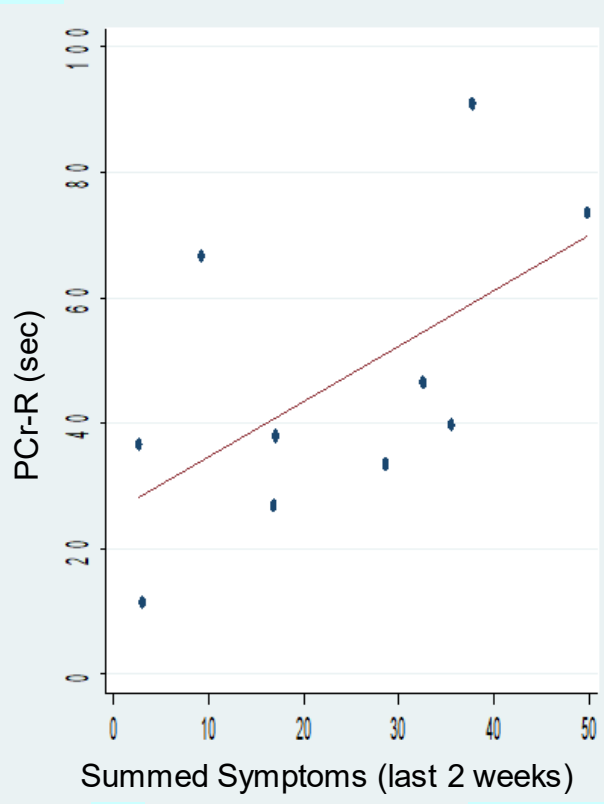
Two Group Stratification		
	Weakness Rated 0-5	Weakness Rated 6-10
	N=7	N=13
PCr-R, Mean (SD)	31.1 (6.95)	45.4 (13.0)
P for difference	**0.01**	

Three Group Stratification			
	None/Low Weakness (rated 0-4)	Intermediate Weakness (rated 5-7)	High Weakness (rated 8-10)
	N=4	N=8	N=8
PCr-R, Mean (SD)	29.9 (7.1)	38.2 (8.9)	47.8 (15.2)
P*	**0.02**		

* Trend across ordered categories

Controls: PCr-R Tied Headache

Controls with recent headache + multiple symptoms had greater PCr-R



Excludes those with summed symptoms of 0

Univariable Prediction of PCr-R in controls

Symptom	Regression with robust SE				Correlation	
	β	SE	P	R^2	R	P
Headache (last 2 weeks)	27.6	10.1	**0.015**	0.43	**0.66**	**0.003**
Sum of all rated symptoms	0.63	0.25	**0.023**	0.30	**0.54**	**0.020**

Conclusions

- Mt/BioE impairment in VGWI: Confirmed.
- Case-Control selection criteria matter! Expansion beyond ideal features enabled documentation of importance of selection choices.
- Muscle weakness tied to PCr-R in VGWI: Heteroplasmy!
  - In mt disease, must match organ *tested* to organ *with symptoms*.
- Headache & multiple symptoms can point to mt/BioE impairment in non Gulf-deployed "controls."[1-3]
  - HA/mult sx: not suitable controls.
- Sex/ethnicity matter -- also in other GWI studies.
- Biomarker properties: 1. All GWI? Best if muscle sx (heteroplasmy!) 2. GWI Nature: Metabolic (Mt/BioE). 3. Rx implications: Yes, documented (CoQ10)[4]. 4. Dynamic biomarker? Expect yes. CoQ10 ↑ PCr on ^{31}P-MRS in mt pts w/ low PCr[5].

1. Sparaco M. *Cephalalgia*. 2006;26(4):361-72. 2. Lantéri-Minet M. *Rev Neurol* (Paris). 1996;152(4):234-8. 3. Finsterer J. Clin Neurol Neurosurg. 2018;166:44-9. 4. Golomb BA. *Neural Comput* 2014;26:2594-651. 5. Barbiroli B. *Cell Mol Bio* 1997; 43 (5): 741-9.

VGWI = Veterans with Gulf War illness

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