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Mitochondrial Peptides and Chronic Fatigue

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ABOUT

Jamie Kunkle, ND
Tickborne Illness & Lyme Disease | Autoimmunity | TCM | Environmental Medicine | Long Covid

Dr. Kunkle has a diverse skill set including (but not limited to): Lyme/infectious disease, autoimmunity, environmental medicine, pain management, hormone regulation, metabolic/weight loss optimization, and neuropsychiatric conditions to name a few. Dr. Kunkle is skilled in low dose immunotherapy and low dose antigen therapy for treatment of allergies, is trained in hyperbaric oxygen therapies, botanical medicine including Chinese herbs, and intravenous/intramuscular nutrition. Dr. Kunkle is an active member of International Lyme and Associated Diseases Society (ILADS).

Dr. Jamie Kunkle ND has been practicing as a dual licensed Naturopathic Doctor and East Asian Medicine Practitioner (Acupuncturist) for 10 years. He currently holds a Naturopathic Doctor's license in California and will be pursuing acupuncture licensure in the future. He recently practiced primary care and infectious disease management in Brattleboro, Vermont where lyme disease and co-infections are endemic. Dr. Kunkle received a Bachelors of Science in Neuroscience from the University of Pittsburgh. He received his masters in acupuncture and traditional Chinese medicine and doctorate in Naturopathic Medicine at Bastyr University in Seattle, WA.

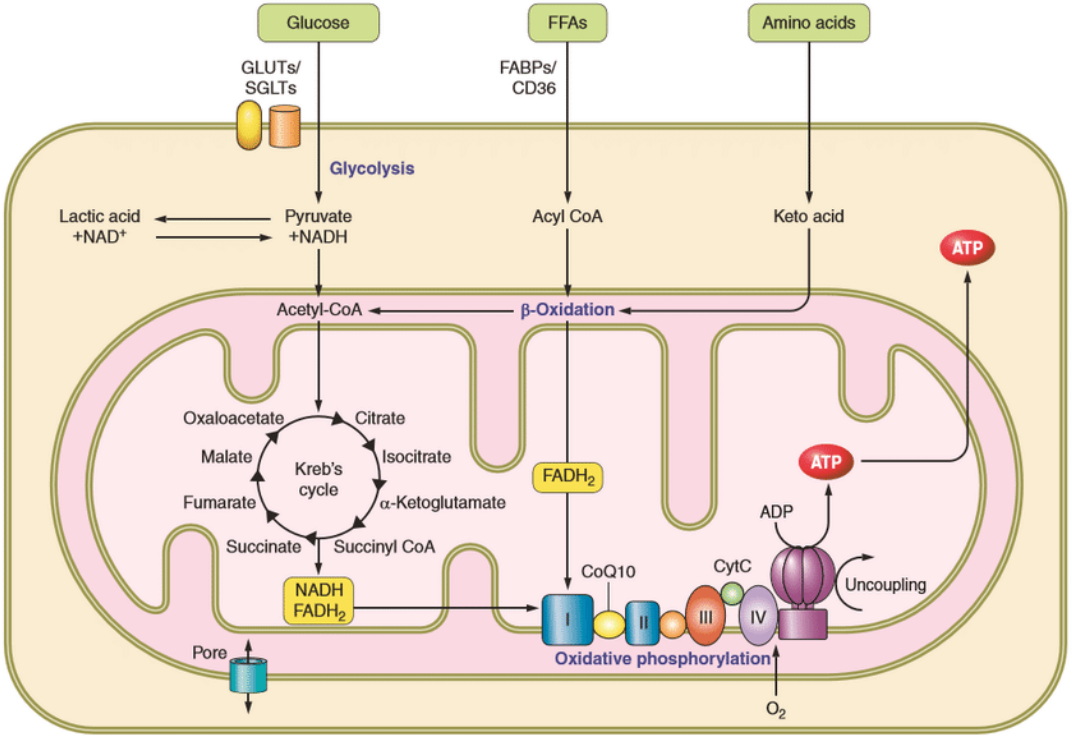
WHAT WE WILL COVER

- Possible causes of mitochondrial dysfunction in chronic illness
- Defining mitochondrial peptides and their utility in chronic fatigue manifestations
- Timing considerations when using these peptides
- Adjunct support and ways to optimize efficacy of peptide treatment
- Other peptides that may compliment mitochondrial peptides
- Dosing considerations: frequency, timing and pulsing strategies
- Case study discussion

Why Are Mitochondria Important in Chronic Fatigue?

- Mitochondria efficiently process the food we eat into fuel (in form of ATP)
- Fuel sources include sugars/carbohydrates, Fat/lipids and protein/Amino Acids (less preferable)
- Mitochondrial disorders are generally linked to chronic fatigue manifestations due to impaired energy production
- Fatigue is typically persistent, debilitating and unrelieved by sleep and rest
- Common Symptoms: weakness, post exertional malaise (PEM), brain fog/neurocognitive disorders, digestive issues

What are the Important Elements of Energy Production?



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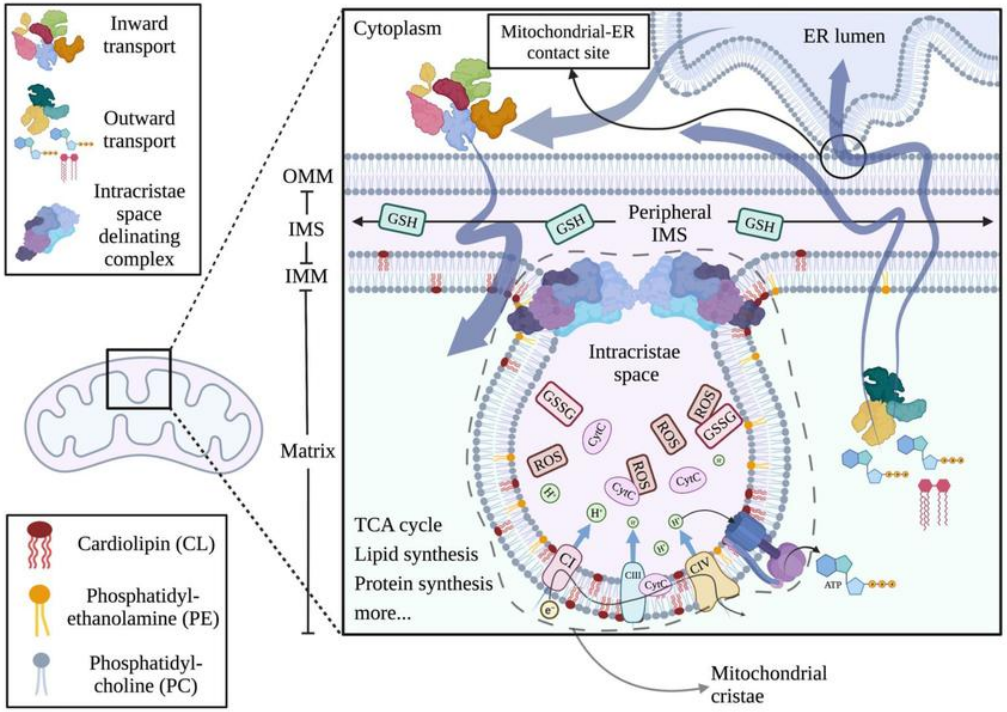
What is Cardiolipin and Why is it Important?

- The mitochondria has TWO cell membrane structures (inner and outer) consisting of phosphatidylcholine (PTC), phosphatidylethanolamine and cardiolipin
- Cardiolipin is a unique phospholipid found in the inner mitochondrial membrane playing a critical role in maintaining mitochondrial structure and function
- Vital for optimizing the activity of respiratory chain complexes and ATP synthase enzymes
- Acts as a mitochondrial “quality control” for mitochondrial fission, fusion, biogenesis, mitophagy (removal of damaged mitochondria), protein import
- Signals responses to cellular stress and damage by recruiting proteins involved in apoptosis (programmed cell death), mitophagy, inflammatory signaling

Cardiolipin and Phospholipids in Mitochondria



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What Are the Common Triggers of Chronic Fatigue?

- Infections: Herpesvirus family (EBV, CMV, HHV-6 and the rest), COVID-19 virus and vaccine, Lyme and related infections (babesia), OTHER viruses (parvovirus B19, Coxsackie, influenza and many others)
- Toxins: mycotoxins (mold), heavy metals, other environmental factors
- Immune Dysregulation: Excess cytokines, autoimmune manifestations, mast cell disorders
- Physical Injury: head (concussions) and neck injuries most common
- Dysautonomia: from any of the above, also post traumatic responses (can be triggered by severe mental/physical stress)
- Endocrine disorders (hormone imbalances): thyroid, adrenals, sex hormones, diabetes/insulin etc.
- Other medical conditions: gastrointestinal disorders, sleep disorders, anemia and many others

Mitochondrial Testing

- Standard is muscle biopsy– most people do not do this
- Alternative: Mito swab or similar (buccal/cheek sample) measuring mitochondrial enzymes and relative complex I-IV activity
- Blood Biomarkers (not an exhaustive list): carnitine free/total, lactate and LD isoenzymes, glutathione and mediators, MDA and lipid peroxidation markers, circulating mitochondrial DNA

Advances in Mitochondrial Testing (AONM)

- The Academy of Nutritional Medicine (AONM) offers specialized mitochondria testing in partnership with a German laboratory called Magdeburg Molecular Detections (MMD).
- Testing focuses on measuring mitochondrial function with advanced techniques such as extracellular flux analysis which is considered gold standard for mitochondrial activity measurement
- Purpose is to diagnose and understand mitochondrial dysfunction and customize personalized treatment planning
- This is a standard blood sample sent out to Germany for analysis

AONM Testing Options

- ATP Profile: Measures total ATP production differentiating mitochondrial ATP from glycolytic ATP (outside mitochondria). This indicates cellular energy capacity.
- Mitochondrial Health Index (MHI): Combines several parameters including basal respiration, ATP turnover, proton leak, maximum respiration, ATP turnover, non-mitochondrial respiration rates to give an overall mitochondrial function score
- OTHER biomarkers: mitochondrial DNA to nuclear DNA ratios, PGC-1alpha, NRF-2, mitochondrial deletion mutations, lactate/pyruvate ratios
- Mitochondrial fuel pathways and Oxidative phosphorylation testing

What Are the Main Mitochondrial Peptides?

- Also known as mitochondrial-derived peptides (MDPs)
- Defined as small bioactive peptides encoded by short open reading frames (SORFs) within the mitochondrial DNA
- Play important rules in cellular metabolism, stress response and intracellular signaling (beyond mitochondria)

- Common Peptides include:
  - MOTS-C
  - Humanin and Small Humanin-Like Peptides (SHLPs 1-6)
  - SS-31 (cardiolipin)

MOTS-C Peptide

- A 16-amino acid peptide coded from the 12S rRNA gene
- Encourages mitochondrial biogenesis (increases their numbers)
- Regulates metabolism, enhances insulin sensitivity, mimics effects of exercise (increase GLUT-4 uptake into muscle)
- Acts as a signaling molecule moving from mitochondria to nucleus to regulate gene expression related to metabolism and stress response

Dosing Considerations:

- 5-15 mg weekly divided into 2-3 doses (Monday, Wednesday, Friday) taken first thing in morning on empty stomach or 30-60 min before fasted cardio (for metabolic optimization)

MOTS-C Peptide

- MOTS-c can translocate into the nucleus in response to metabolic stress and regulation of adaptive nuclear gene expression.
- This allows the peptide to promote resistance of metabolic stress by upregulating the mitochondrial genome.
- Upregulating these genes encourages mitochondrial biogenesis.
- MOTS-c inhibits the methionine-folate cycle resulting in purine synthesis, increase in PCG-1α (a key regulator of energy metabolism), and AICAR (5-Aminoimidazole-4-carboxamide ribonucleotide)accumulation which activates AMPK (5'- adenosinemonophosphate-activated protein kinase). This acts as an energy sensor by monitoring the ratio of AMP and ATP.
- AMPK (AMP-activated protein kinase) restores homeostasis by initiating catabolic processes for ATP production in case of energy deficits.

Humanin Peptides

- A 24-amino acid peptide encoded within the 16S rRNA region of mitochondrial DNA.
- Has cytoprotective effects, protecting cells from apoptosis and oxidative stress
- Has roles in neuroprotection and metabolic regulation
- Promotes glycolysis, ATP production and mitochondrial biogenesis to help cells survive energetic stressors
- Anti-inflammatory: reduces TNF-alpha and IL-6
- Short half life drug (30 min)

Dosing Considerations:

- 5-10 mg per week divided into 2-3 injections (Monday, Wednesday, Friday) 2-4 weeks on 2-4 weeks off
- Common: 2 mg every other day
- Side effects: mild usually

Humanin Like Peptides

- Related Peptides:
  - Small humanin like peptides (SHLPs 1-6)
  - Varying functions pending on number: example SHLP2 promotes mitochondrial biogenesis while SHLP6 induces apoptosis (programmed cell death)

SS-31 (Elamipretide)

- SS-31 is a synthetic mitochondria-targeting tetrapeptide that selectively accumulates in the inner mitochondrial membrane by binding to cardiolipin (stabilizing cristae structure)
  - Inhibits permeability pores (leakiness), reduces cytochrome C release (prevents damage)
- It has been shown to protect and restore mitochondrial structure, improve ATP production and reduce oxidative stress by scavenging reactive oxygen species (ROS)
- SS-31 helps to optimize the electron transport chain (ETC) and cardiolipin function

- DOSING Considerations: 1-5 mg daily or every other day (4 mg daily for 20 days)
- Side effects: generally considered mild in study models

SS-31 (Elamipretide)

NOTE:

- Some mitochondria penetrating peptides (MPPs) MAY have benefits in babesia and malarial infection– (MPP enters mitochondria in malaria infected red blood cells potentially killing parasite in blood stage without disrupting host membranes)–
- I am unable to find evidence that SS-31 has any antimicrobial activity.
- Here is a paper studying mitochondrial penetrating peptides acting as possible antimalaria targets (peptide itself or as a possible piggyback to drug therapies):
- Somsri S, Mungthin M, Klubthawee N, Adisakwattana P, Hanpithakpong W, Aunpad R. A Mitochondria-Penetrating Peptide Exerts Potent Anti-Plasmodium Activity and Localizes at Parasites' Mitochondria. *Antibiotics*. 2021; 10(12):1560. https://doi.org/10.3390/antibiotics10121560

General Treatment Considerations

- Preparing for mitochondrial therapies:
- Cellular Detoxification (heavy metals, mycotoxins, pesticides, various pharmaceuticals) and nutrient repletion (vitamins/minerals, phospholipids, vitamin C etc.)
- Gut work– many people with inflamed guts do NOT absorb vital mitochondrial minerals and vitamins, systemic inflammation may be originating in the gut even if manifesting elsewhere
- Co-treating or ideally pre-treating viruses and intracellular infections (Lyme)
- Dysautonomia support (comes in many forms but vital to this process)
- Hormone/endocrine support (thyroid, adrenals, sex hormones especially)

- Rotations of mitochondrial peptides: MOTS-C rotating with humanin and SS-31

Complimentary Peptides

- Immune Modulators: Thymosin alpha-1, thymosin beta-4, thymulin
- Antimicrobial peptides: LL-37, KPV
- Neuroinflammation and autonomic support: Selank, semax, Cerebrolysin, oxytocin, melanotan 2, Vasoactive intestinal peptide (VIP), ARA-290
- Nootropic support: Dihexa
- Gut barrier support: BPC-157, larazotide, KPV
- Connective tissue support: BPC-157, GHK-Cu
- Mast Cell Support: KPV, TB4 frag, Amlexanox
- Sleep support peptides: DSIP, pinealon, epithalon, GH modulators
- Growth hormone secretagogues: CJC, ipamorelin, sermorelin, tesamorelin, AOD 9604 and many more
- Bioregulators in general

Case Study

- 65 year old patient with long history of chronic fatigue, dysautonomia secondary in part to chronic infections (Lyme associated chronic illness with viruses: EBV, CMV, coxsackie)
- Grew up in dysfunctional family, multiple ACES
- Bitten by a tick at age 20, diagnosed with fibromyalgia in late 20s (manifested as severe pain and extreme fatigue—exercise intolerance and post exertional symptoms)
- History of head injuries (2), SVT (ablation in 2000)
- Hospitalized in 2016– overnight developed POTS overnight and was essentially bedridden with severe fatigue, unable to work
- Agents established for POTS/dysautonomia: DNRS, meds (beta blockers, alpha blockers, fludrocortisone), muscle relaxer for pain/fibro symptoms
- Meds that have helped: Antibiotics (minocycline), antivirals (Valacyclovir, Valganciclovir, Sophora/Ku Shen recently)

Case Study

What worked finally:

- Combination of antivirals and mitochondrial therapies (started with typical nutrients, NAD, methylene blue, earlier on poly MVA but ultimately addition of mitochondrial peptides made all the difference)

- “Hello. I wanted to give you a quick update. I started the MOTs-C on 5/5. I finished two vials in May and just started my 3rd vial. I can definitely see an upward trend in energy with some ups and downs in between. I started the Humanin on 5/19. I also started the NMN, the TMG powder and a Methylated B-Complex. I am encouraged with my increase in energy.”

- Peptide Rotation:
- MOTS-C 2 mg every other day or as needed (more than 2 mg will affect sleep)
  - Max 5-10 mg per week for maintenance ultimately
- Humanin 1-2 mg 2-3 days per week (alternating)
- SS-31: 4-5 mg every other day for 3 months with phospholipids

Case Study

“Overall, I've been doing really well. The Mots-C has been such a game changer for me. I subbed about 15 days last month and I feel, for the most part, like a normal person.”

Patient was able to go back to work and takes MOTS-C as needed when fatigue is worsening.
Intermittent immune support (we still use thymosin alpha-1 and antivirals as needed)
Recently she was in a major flare and we started oxymatrine (extracted from sophora root) and increased peptides, improvements was significant and she was back to baseline within two weeks.

UPDATE: “Started oxymatrine-- TWO days after we spoke-- Within TWO days could feel fatigue lifting--
Wondering if it was placebo effect-- normally does not believe anything will work so maybe it was helpful-- Within 4-5 days, felt 80% normal--
It was SHOCKING how much better I felt--Had just started subbing summer school-- was able to sub for at least 5 hours per day so was not a full day– “

CONCLUSION

- Mitochondrial therapies alone may not be effective if there are still significant cellular stressors present within the system
- Per usual have to treat the individual (the whole person), no stone left unturned
- Advanced testing is improving every year to find more objective measures to help guide treatment
- There is always hope but chronic fatigue takes a multifaceted approach and quite a bit of persistence to find answers and effective therapies