Brain Mitochondrial Metabolism and Psychiatric Illness

Benjamin Brown, ND
timeforwellness.org
Energy Production

**DIET**
Carbohydrates, fats, proteins.

**OXYGEN**

**ATP**
Energy
No more ‘Qi’

“Mitochondrial dysfunction, characterized by a loss of efficiency in the electron transport chain and reductions in the synthesis of high-energy molecules, such as adenosine-5’-triphosphate (ATP), is a characteristic of aging, and essentially, of all chronic diseases.”

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Mitochondrial dysfunction, characterized by a loss of efficiency in the electron transport chain and reductions in the synthesis of high-energy molecules, such as adenosine-5’-triphosphate (ATP), is a characteristic of aging, and essentially, of all chronic diseases. These diseases include neurodegenerative diseases, such as Alzheimer’s disease, Parkinson’s disease, Huntington’s disease, amyotrophic lateral sclerosis, and Friedreich’s ataxia; cardiovascular diseases, such as atherosclerosis and other heart and vascular conditions; diabetes and metabolic syndromes; autoimmune diseases, such as multiple sclerosis, systemic lupus erythematosus, and type 1 diabetes; neurodegenerative and psychosomatic diseases such as gastrointestinal disorders; and fatigue and other symptoms of disease can naturally restore, even in long-term patients with the Ther Health Med. 2013;19(9):#.

It is well known among researchers that mitochondrial genetic or primary mitochondrial disorders contribute to mitochondrial dysfunction as well as secondary or acquired degenerative disorders. This review will concentrate on non-genetic or acquired mechanisms that could explain mitochondrial dysfunction and their replacement treatment with natural supplements and combinations of natural supplements, including vitamins, minerals, enzyme cofactors, antioxidants, metabolites, transporters, membrane-type phospholipids, and other natural supplements.

MITOCHONDRIAL MOLECULAR DYSFUNCTION

Mitochondrial dysfunction arises from an inadequate number of mitochondria, an inability to provide necessary substrates to mitochondria, or a dysfunction in their electron transport and ATP-synthesis machinery. The number and functional status of mitochondria in a cell can be changed by (1) fusion of partially dysfunctional mitochondria and reduction of their number, or (2) communication between...
Dysfunctional DIET
- Carbohydrates, fats, proteins.

OXYGEN

INFLAMMATION

OXIDATIVE STRESS

LESS ENERGY (ATP)

✓ Impaired metabolism
✓ Dysfunction
✓ Chronic disease

Dysfunction and deadly
“At the cellular level, moderate to severe fatigue is related to loss of mitochondrial function and diminished production of ATP.”
Brain burnout

“Deficits in mental energy, defined as measures of mood, motivation and cognition, may significantly affect quality of life in a large portion of the general population. Central to the maintenance of optimal mental energy is the role of the mitochondria in energy metabolism in the central nervous system.”

Mitochondrial psychiatry

“Brain mitochondria are essential for neurotransmission, short- and long-term neuronal plasticity, cellular resilience to stress and behavioural adaptation. Dysfunction in these metabolic processes contributes to a wide variety of diseases, including psychiatric disorders.”
Mitochondrial-related neurodegenerative and psychiatric disorders:

- Autism
- Depression
- Bipolar disorder
- Anxiety disorders,
- Obsessive-compulsive disorder
- Schizophrenia
- Ageing and senescence
- Alzheimer’s disease

“...we think that many of the upstream abnormalities (which are probably encoded by the nuclear genome) in psychiatric disorders converge to impair mitochondrial function, resulting in abnormalities in synaptic plasticity and long-term cellular resilience.”

Impaired mitochondrial function in psychiatric disorders


functions of mitochondria in the brain

the main functions of mitochondria, described above, are essential for neurotransmission, short-
Opportunity

"...the ability to modulate mitochondrial function may have an important role in regulating synaptic strength and cellular resilience in neuronal circuits that mediate complex, high-order brain functions such as cognition, affect, perception and behaviour."

Impaired mitochondrial function in psychiatric disorders

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Impaired mitochondrial function in psychiatric disorders
Missed opportunity

Psychotropic medications and mitochondrial toxicity

Rebecca Anglin, Patricia Rosebush and Michael Mazurek

In a recent review, Husseini Manji and colleagues highlighted missed opportunities in the much wider population of patients receiving treatment with these agents for psychiatric conditions. Multiple studies have shown that both typical and atypical antipsychotics contribute to mitochondrial dysfunction. One of the often-overlooked contributors to mitochondrial dysfunction is the psychotropic medication used to treat these psychiatric conditions.

“This under-recognized mitochondrial toxicity may contribute to the limited efficacy and problematic side effects of many psychotropic medications, not only in those with mitochondrial disorders but also in the much wider population of patients receiving treatment with these agents for psychiatric illness.”

Nat Rev Neurosci. 2012 Sep;13(9):650.
"Mitochondrial nutrients have been defined as nutritional compounds that (1) enter the cells and mitochondria following exogenous administration, (2) protect the mitochondria from oxidative damage, and (3) improve mitochondrial function."
Whole-of-diet

"Non-pharmacological approaches to the treatment of depression and anxiety are of increasing importance, with emerging evidence supporting a role for lifestyle factors in the development of these disorders. Observational evidence supports a relationship between habitual diet quality and depression."

Brain Food: Diet and Mental Health

Natural Diet:
Phytonutrient Dense, Caloric Shortage

- Neuroprotection
- Neurogenesis
- Synaptic Plasticity

Modern Diet:
Phytonutrient Poor, Caloric Excess

- Cell Damage
- Cell Death
- Impaired Plasticity

Cognition/ Mood/ Behavior:
- Optimism
- Cognitive Resilience
- Enthusiasm
- Vigor and Energy

Cognition/ Mood/ Behavior:
- Depression
- Cognitive Decline
- Hostility
- Fatigue and Malaise
“Because it evolved, in part, for success in seeking and acquiring food, the brain functions best when the individual is hungry and physically active, as typified by the hungry lion stalking and chasing its prey. Indeed, studies of animal models and human subjects demonstrate robust beneficial effects of regular exercise and intermittent energy restriction/fasting on cognitive function and mood, particularly in the contexts of aging and associated neurodegenerative disorders.”
"...we used nuclear magnetic resonance spectroscopy to show that during aging caloric restriction (CR) preserves mitochondrial energy production, energy demand, and neuronal activity with a long-lived rodent model. These results provide a rationale for CR-induced sustenance of brain health with extended lifespan."

J Cereb Blood Flow Metab. 2014 Sep;34(9):
Neurohormesis

“From an evolutionary perspective, the noxious properties of such phytochemicals play an important role in dissuading insects and other pests from eating the plants. However, at the relatively small doses ingested by humans who consume the plants, the phytochemicals are not toxic and instead induce mild cellular stress responses.”
Mild Stress
(dietary phytochemicals)

Hormetic Response Pathway
(Ion channels, kinases, deacetylases, transcription factors)

Stress Resistance Proteins
(Heat shock proteins, antioxidants, growth factors)

Response vs. Dose

Survival vs. Dose

Area of Hormesis
(Adaptive stress response)

Deficiency

Toxicity

Dose

Neuromolecular Med.
2008;10(4):
Diet and exercise can affect cellular metabolic activity, which can influence neuronal plasticity and cognitive processes.

Ketosis

"The state of ketosis is a normal physiologic state that occurs during fasting and carbohydrate restriction, and also normally occurs in newborns. It is beneficial because it derives energy from fatty acid oxidation that results in the formation of ketone bodies. Importantly, some of the beneficial neurometabolic effects of ketogenic diets may also be achieved without any significant dietary restriction, by adding ketone bodies to the diet."
“Following calorie restriction or consumption of a ketogenic diet, there is notable improvement in mitochondrial function, a decrease in the expression of apoptotic and inflammatory mediators and an increase in the activity of neurotrophic factors.”
"We randomly assigned 23 older adults with mild cognitive impairment to either a high carbohydrate or very low carbohydrate diet. Following the 6-week intervention period, we observed improved verbal memory performance for the low carbohydrate subjects as well as reductions in weight, waist circumference, fasting glucose, and fasting insulin."
Coconut Oil

During the 4-week study people with moderate to severe Alzheimer’s disease added 20 grams (about 1.5 tablespoons) of virgin coconut oil to their regular diet while maintaining their regular medication.

*Coconut oil had significant beneficial effects on cognitive performance* within 2-weeks, with a bigger effect after the 4-weeks and the effects were even sustained for at least 2-weeks after they stopped taking the oil.

The majority of the study participants caregivers also observed improvements in alertness, expression of language, overall activity and mood.

Qi-Nutrition

DIET
Carbohydrates, fats, proteins.

OXYGEN

Acetyl-L-carnitine
Alters mitochondrial lipid membrane and metabolism

Multivitamins
Broad-spectrum mitochondrial nutrients

Creatine
Improves bioenergetics and membrane structure

Omega-3
Vital for membrane function and resilience

CoQ10
Restores dysfunctional mitochondria

ATP
Energy
Qi-Nutrition

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Acetyl-l-carnitine

Four randomized clinical studies (RCT) demonstrated the superior efficacy of acetyl-l-carnitine (ALC) over placebo (PBO) in patients with depression. Two RCTs showed its superior efficacy over PBO in dysthymic disorder, and 2 other RCTs showed that it is equally effective as fluoxetine and amisulpride in treatment of dysthymic disorder. ALC was also effective in improving depressive symptoms in patients with fibromyalgia and minimal hepatic encephalopathy. It was also found to be equally tolerable to PBO and better tolerable than fluoxetine and amisulpride.

J Psychiatr Res. 2014 Jun;53:30-7
Re-energize

1. Low brain energy (phosphocreatine [PCr]) levels in a depressed person

2. Brain energy levels increased after with acetyl-l-carnitine and depressive symptoms diminished

Pettegrew JW, et al. 31P-MRS study of acetyl-L-carnitine treatment in geriatric depression: preliminary results
Qi-Nutrition

**Acetyl-l-carnitine**
Alters mitochondrial lipid membrane and metabolism

**Multivitamins**
Broad-spectrum mitochondrial nutrients

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**OXYGEN**

**ATP**
Energy
Multivitamins

“We are at a tipping point in psychiatry. With few psychiatric drugs on the horizon and long-term studies suggesting medication may do more harm than good, it is time to revisit the very old idea that nutrition can have a positive effect on mental health.”

There are now over 20 placebo-controlled RCTs showing the benefit of multinutrients in treating stress, anxiety, aggression in prisoners, low mood, autism and ADHD.
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Creatine

“Impairments in creatine metabolism have also been implicated in the pathogenesis of psychiatric disorders, leaving clinicians, researchers and patients alike wondering if dietary creatine has therapeutic value for treating mental illness.”
Exogenous creatine supplementation has been shown to reduce neuronal cell loss in experimental paradigms of acute and chronic neurological diseases. In line with these findings, first clinical trials have shown beneficial effects of therapeutic creatine supplementation.
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Qi-Nutrition

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**CoQ10**
Restores dysfunctional mitochondria

**ATP**
Energy
CoQ10

“A relationship exists between lowered CoQ10 levels and elevated immune-inflammatory and oxidative and nitrosative stress pathways and mitochondrial dysfunction and the generation of specific symptoms/behaviors, including fatigue, hyperalgesia, and depression, and the onset of neurodegenerative processes.”

An important clinical improvement was evident after CoQ10 versus placebo treatment showing a reduction of FIQ, and a most prominent reduction in pain, fatigue, and morning tiredness subscales from FIQ. Furthermore, we observed an important reduction in the pain visual scale and a reduction in tender points, including recovery of inflammation, antioxidant enzymes, mitochondrial biogenesis, and AMPK gene expression levels, associated with phosphorylation of the AMPK activity.
In an open label study, CoQ10 treatment (400 mg/d titrated up by 400 mg/d every 2 weeks to a maximum of 1200 mg/d) resulted in a trend towards improved the forward rate constant \((k_{\text{for}})\) of creatine kinase (CK) and a reduction in depression symptom severity.

**Keywords**

bipolar depression, CoEnzyme Q10, mitochondria, geriatric, magnetic resonance spectroscopy (MRS)

**Introduction**

Depression is the predominant phase of bipolar illness throughout the life cycle, yet disease mechanisms remain unclear, and resistance or nonresponse to current treatments is high. Published studies of individuals with bipolar disorder implicate the pathogenic role of altered cerebral bioenergetic pathways. Specifically, phosphorus magnetic resonance spectroscopy (MRS) studies have indicated reduced levels of phosphocreatine (PCr) and increased levels of phosphomonoesters (PME) in frontotemporal and parietal gray matter in bipolar patients compared to healthy controls.
Coenzyme Q10 regulates serotonin levels and depressive symptoms in fibromyalgia patients: results of a small clinical trial

To the Editors:

Increased serum 

CoQ10 and serotonin levels in platelets from FM patients were restored in the COQ10-treated group compared to placebo group. Interestingly, a notable improvement in depressive symptoms evaluated with the BDI scale was also observed in the CoQ10-treated group compared to the placebo group.

The study protocol was reviewed and approved by the Ethical Committee of the University of Seville. All the participants of the study gave their written informed consent before initiating the study. This study was carried out in compliance with the Declaration of Helsinki, and all the International Conferences on Harmonisation and Good Clinical Practice Guidelines. Twenty patients diagnosed with FM were distributed in a clinical trial as described in Cardona et al. The patients were diagnosed with FM by exclusion of other diseases and syndromes, and in accordance with the American College of Rheumatology criteria. Subjects were randomized in a double-blind fashion. In the CoQ10-treated group compared to placebo group, a beneficial effect of CoQ10 on serotonin levels in platelets was observed in the 24-hour samples collected under fasting conditions and platelets were isolated. CoQ10 levels were determined by HPLC and serotonin levels by COMT assay (Pratikten). The results show that CoQ10 significantly increases serotonin levels in platelets and, presumably, in other cells, such as neurons of the central nervous system. CoQ10 is an important component of the mitochondrial respiratory chain enabling the generation of adenosine triphosphate by oxidative phosphorylation. Because adenosine triphosphate levels have been observed to be reduced in platelets from FM patients and FM has been related with alterations in the hypothalamic-pituitary-adrenal (HPA) axis, and hormone and neurotransmitter secretion, a possible explanation for our results is that CoQ10 may play an essential role in the regulation of neurotransmitters status in platelets and in other cells such as neurons of the central nervous system and thus, it may affect serotonin content, transmission, and function. These results may also contribute to explain the antidepressant effect of CoQ10 treatment. Our findings also highlight the importance of CoQ10 supplementation as an alternative therapy for controlling depression. Further analyses involving more patients in a double-blind placebo-controlled clinical trials are required to confirm these observations. Indeed, our research group is currently working in this direction, based on the conclusions of the exploratory information discussed in this article.

AUTHOR DISCLOSURE INFORMATION

The authors declare no conflicts of interest.

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CoQ10 & serotonin

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Cardiolipin

✓ Mitochondrial membranes contain high levels of cardiolipin, a tetra-acyl phospholipid

✓ Cardiolipin comprises 10–20% of the mass of total mitochondrial phospholipid

✓ Depletion of cardiolipin results in severe mitochondrial dysfunction

✓ Supplementation with n-3 PUFA increases membrane phospholipid DHA and depletes arachidonic acid, and can increase cardiolipin

Remodeling

Omega-3 supplementation [2 g eicosapentaenoic acid (EPA) and 1 g docosahexanoic acid (DHA) per day] for 12 weeks of leads to a remodeling of the mitochondrial membrane with significant incorporation of omega-3 fatty acids into various phospholipid species and displaces omega-6. Mitochondrial ADP sensitivity and maximal mitochondrial ROS emission were also increased.

E. A. F. Herbst1, S. Pagliautunga1, C. Gerling1, J. Whitfield1, K. Mukai1, A. Chabowski1, G. J. F. Heigenhauser1, L. L. Spriet1 and G. P. Holloway1
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Sub-chronic administration of fish oil for three weeks restored the age-related decrease in respiration and improved ATP production and enhanced the levels of Bcl-2 protein and NPD-1-like metabolites.

Mitochondrial proteins of the Bcl-2 family are important regulators of the intrinsic apoptotic pathway and have been directly implicated in mitochondrial function. NPD-1 is a DHA metabolite that promotes cell survival via the induction of anti-apoptotic and neuroprotective gene expression.
 Omega-3 index

“A higher omega-3 index has been correlated with larger total normal brain volume and hippocampal volume, lower depressive symptoms, and better neurocognitive performance under stress.”

JOM, 2014; 29(3): 115-122
Brain Food: Diet and Mental Health

Natural Diet: Phytonutrient Dense, Caloric Shortage
- Neuroprotection
- Neurogenesis
- Synaptic Plasticity

Modern Diet: Phytonutrient Poor, Caloric Excess
- Cell Damage
- Cell Death
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“...when treating secondary/acquired mitochondrial disorders, we obviously have to “think outside of the mitochondria” to address the cause(s) of the mitochondrial impairment, most commonly arising from various combinations of nutrient deficiencies, carbohydrate excess, toxin exposures, and microbial colonizations.”