Minding the Mitochondria: From Cell to Psyche

Susana A. Galle, PhD, MSCP, ABMP, CTN, CCN, DHM, CCH, BCN, RYT
Director, The Body-Mind Center, Washington, DC
Medical/Prescribing Psychologist, Albuquerque, NM

“In nature we never see anything isolated, but everything in connection with something else which is before it, beside it, under it and over it.”

Johann Wolfgang von Goethe (1749-1832)

Abstract
This article links mitochondria and the mind. Mitochondria, our intracellular energy factories, contain a genetic blueprint, utilize nutrients, and provide metabolic fuel for neuroendocrine and immune processes that lead to health or disease. The mind constantly interacts with those processes, in a social context replete with epigenetic factors. Medications also affect the energy cycle, increasing the complexity of that biopsychosocial equation. The review of mitochondrial function focuses on stress and psychiatric disorders. Research and clinical examples demonstrate the effectiveness of mitochondrial support through nutrition with psychiatric patients. Moreover, the mind-brain-gut connection is a key factor in energy production and utilization. From this author’s perspective, the mind impacts mitochondrial function through self-regulation and mental changes generated by psychotherapy and metabolic nutrition. Psychophysiological measurements and molecular nutrition testing hold promise for assessing the mind-mitochondria links and treating their derailments. This holistic model generates hypotheses for research and evidence-based clinical work.

1. Introduction
2. Mitochondria and their Functions
   Figure I: Structure of a Mitochondrion
   Figure II: Mitochondria and the Energy Cycle
3. Mitochondria and Neurotransmission
4. Mitochondria in Relation to Disease and Aging
5. Stress, Psychiatric Disorders and Mitochondria
6. Mitochondrial Dysfunction in Mood Disorders, Schizophrenia, and Autism
7. Primary Mitochondrial Diseases and Psychiatric Disorders
8. Metabolic Pathway Testing and Mitochondrial Function
9. Metabolic Nutrition for Mitochondrial Therapeutics
10. Classification of Nutrients for Mitochondrial Support
11. Key Mitochondrial Nutrients: Carnitine, CoQ10, and ATP Cofactors (B2, B3)
12. Other Mitochondrial Nutrients
13. Botanicals with Beneficial Effects on Brain Mitochondria
15. Medication-Induced Mitochondrial Dysfunction
16. Gastrointestinal Health and Mitochondria
17. The Mind-Brain-Gut/Energy Connection

Correspondence address: Susana A. Galle, PhD, MSCP, ABMP, CTN, CCN, DHM, CCH, BCN, RYT, The Body-Mind Center, 5443 31st St, NW, Washington, DC 20015-1345, Phone (202) 362-3837, email doctorsusana@gmail.com
18. A Holistic Psychotherapeutic Matrix for Mitochondrial Support

19. Closing Remarks and Future Directions:
   a) Ideas for a Biopsychosocial/Energy-Oriented Practice
   b) Linking Mitochondria and Psyche: What is Next?

20. Epilogue - Minding the Mitochondria: the Chinese Way

Key words: mitochondrial function, metabolic nutrition, mind-brain-gut connection, psychotherapeutic matrix

Introduction

It takes a village to build bridges between cell and psyche... This work illuminates that path. Mitochondria are pillars of physiology and metabolism, constituting a dynamic substrate of mental and behavioral expression. While genes create road maps, nutrients fertilize the terrain and the mind cultivates it. Nutrition “feeds” the nervous system, including axonal and synaptic aspects. In the presence of vitamins, minerals and enzymes, mitochondria metabolize the brain’s main fuel, glucose, into energy intermediates needed to synthesize and release neurotransmitters. The interplay of neurotransmitters, hormones, and immune processes influences the mind. The latter is shaped by social interactions and, in turn, reshapes that interplay. Psychotropic drugs, as mind-modifying agents, affect energy metabolism as well. This monograph references research and clinical illustrations reflecting the value of mitochondrial support through nutrition with psychiatric patients. Conversely, the mind’s impact on energy metabolism is considered in relation to improved self-regulation and mental changes through holistic psychotherapy. At the close, there is a rich harvest of takeaway pearls. An outline of issues for further query follows, when minding the mitochondria.

Mitochondria and their Functions

Mitochondria (fr. Greek, mito= thread; chondrion= granule) are rod-shaped, intracellular organelles labeled “powerhouses of life”\(^1\). They are a matter of energy. Energy drives the brain, our main organ of behavior. Mitochondria have different shapes and serve various metabolic functions. They underlie the cascade of metabolic events that sustain the mind. Mitochondrial assessment, moreover, entails various laboratory techniques\(^2\). Today’s genetic research on mitochondria is matched by renewed interest in lifestyle factors modifying gene expression, including mitochondrial function—that is epigenetics. Lifestyle includes what we think, feel, eat, our actions, relationships, environmental exposure, and socioeconomic factors. Nutrigenomics individualizes the use of nutrients, enzymes, cofactors, and diet, quieting the expression of deleterious genes\(^3\). When addressing the whole biopsychosocial matrix in psychotherapy\(^4\), a light shines on interventions that can improve mitochondrial function in concert with mental healing.

Figure 1: Structure of a Mitochondrion
Mitochondria originated from bacteria, most likely parasitic, which were incorporated into our cells through symbiosis at some point in evolution. These battery-like organelles influence neurotransmission, and rely heavily on nutrients. Mitochondria respond to sustained stressors and the psychophysiological states linked to them. Psychotropic drugs also impact mitochondria. Some drugs are beneficial, while others impair mitochondrial function in various body systems\textsuperscript{5,6}. It is a challenge to pin down the mitochondrial damage from specific medications, and minimize those effects through nutrition and/or improved pharmaceuticals. Metabolic pathway testing provides data about mitochondrial function, and guides molecular nutrition interventions. Further, various psychotherapies may help restore mitochondrial health, by promoting autonomic (ANS) balance, cognitive/affective reframing and central nervous system (CNS) reorganization, along with lifestyle changes\textsuperscript{8}. The therapist-patient relationship is an integral part of the healing equation. Psychotherapy, in synergy with metabolic nutrition, forms a foundation for renewable mitochondrial function.

**Energy generation as adenosine triphosphate (ATP)** is the main job of mitochondria. They manufacture 90% of the energy required for growth and to sustain life. For this purpose, a number of proteins are present in its inner membrane. ATP production entails the oxidation of major products found in the cytosol, namely, glucose, pyruvate, and NADH (reduced NAD+ or niacinamide dinucleotide). An electron transport chain (ETC) couples the electron transfer between a high-energy electron donor (e.g. NADH) and an electron acceptor (O\textsubscript{2}) [i.e., oxidative phosphorylation, or OXPHOS], with the transfer of H\textsubscript{+} ions (protons) across the membrane. An electrochemical proton gradient is produced, which in turn is used to generate energy as ATP via the ATP synthase complex. The cell can then utilize or store that energy as needed. The energy cycle is illustrated below:

![Mitochondria and the Energy Cycle](image)

**Figure 2: Mitochondria and the Energy Cycle**
(CAC, TAC, or Krebs Cycle)

Mitochondria also participate in other metabolic functions: regulation of the membrane potential, redox signaling, regulation of free radicals, cell apoptosis and proliferation, calcium...
signaling, as well as steroid synthesis. Furthermore, mitochondria play a part in cell lipid metabolism, signaling, and repair. Some mitochondrial functions only take place in specific types of cells. As an illustration, liver mitochondria are equipped with enzymes to detoxify ammonia in the urea cycle, promoting total health and mental clarity.

The concentration of mitochondria in different organs correlates with varying energy needs. Being the most energy-intensive organ, the heart has the highest number of mitochondria, and the brain follows closely. The muscles, stomach, intestines, and endocrine glands (e.g.; thyroid, pancreas) are highly dependent on mitochondria. There are also kidney tubules densely populated with mitochondria, while platelets and the skin have few. Although there are no mitochondria in mature red blood cells (RBC), their precursor, the proerythroblast, depends heavily on mitochondria during RBC development. A cell with fewer mitochondria is one designed for a lower energy output, unless it is dysfunctional.

Mitochondrion is the only cell organelle with its own DNA (mtDNA), which is passed on through maternal genes. Some research suggested that paternal mtDNA survives in the zygote, contributing to the mtDNA pool of adult human skeletal muscle. However, paternal inheritance of mtDNA is the exception. Mitochondria replicate through cloning, fission, and fusion. Mutations or polymorphisms of mitochondrial DNA (mtDNA), mitochondria-mediated oxidative stress, reduced ATP production, and changes in intracellular calcium characterize several diseases.

Luft first described mitochondrial disorders in 1962, as the disruption of energy metabolism in several pathways, namely:

1. oxidative phosphorylation (OXPHOS);
2. fatty acid oxidation, and/or
3. the energy cycle (CAC, TCA or Krebs Cycle)

Once mitochondria are impaired, organ and systemic effects invariably result.

**Mitochondria and Neurotransmission**

Throughout the nervous system, profuse mitochondria are the hallmark of synapses. Their role in neurotransmission was revealed via fruit fly (Drosophila) studies. Such work pinpointed the sub-cellular events that require mitochondria. Light microscopy showed that the synaptic terminals of axons contain a very high concentration of mitochondria, ushering the modern ultra-structural study of synapses. In the first electronic microscopy studies of the nervous system, synapses were located on the basis of mitochondria density (pre- and post-synaptic). Synapses, like other mitochondrion-rich regions of the neuron, have a high need for ATP and/or calcium buffering. Deficient ATP compromises the energy-intensive endocytosis, exocytosis, and vesicle recycling of the presynaptic region. Post synaptic mitochondria, for their part, rapidly move into dendrite areas where synaptic activity has been stimulated, as shown in studies of the fruit fly’s neuromuscular junction (NMJ).

Neurons depend on mitochondrial function in order to establish membrane excitability, for neurotransmission, and to develop plasticity. Extensive data come from isolated mitochondria and dissociated cell cultures. In contrast, little is known about mitochondrial function within intact neurons in brain tissue. Yet, a clear description of the interactions among mitochondrial function, energy metabolism, and neuronal activity is crucial to understand neurons and their pathophysiology. New fluorescence imaging techniques, electrophysiology, and brain slice preparations examine mitochondrial function during neuronal activity, with high spatiotemporal resolution. One research group assessed mitochondrial calcium transport, membrane potential, and energy metabolism during normal neuronal activity. They also described how mitochondrial and metabolic dysfunction
develop during pathological activity, focusing on temporal lobe epilepsy as their experimental model. In another study, five patients presenting a clinical picture suggestive of neuro-transmitter defects from early infancy on, had underlying mitochondrial diseases. The patients’ symptoms ranged from infantile hypokinetic-rigid syndrome, to various abnormal movements, limb hypertonia, feeding difficulties, and psychomotor delays impairing learning and performance. The diagnosis was based on magnetic resonance imaging (MRI), cerebrospinal fluid (CSF), biogenic amine and pterin measurements, respiratory chain enzyme activity, and molecular assessment. In 3 out of 4 untreated patients, CSF analysis revealed low homovanillate (HVA, dopamine metabolite) and 5-hydroxyindoleacetate (5-HIAA, serotonin metabolite) in 2 of them. L-dopa therapy led to modest improvement. Those new techniques could be expanded to include mitochondrial dysfunction in mental disorders, and open therapeutic avenues.

Mitochondria in Relation to Disease and Aging

Since the 1960s, there has been major progress towards understanding mitochondria in relation to health, disease, and aging. Mitochondrial disorders are increasingly acknowledged as a major category in clinical neurology, both in relation to altered mtDNA and coenzyme Q10 deficiency. However, several mitochondrial diseases express themselves outside the CNS and peripheral neuromuscular system. These include the heart, endocrine system, liver, kidneys, blood, and gastrointestinal (GI) conditions. An emerging body of knowledge links mitochondrial dysfunction to metabolic and non-metabolic abnormalities. Among those conditions are: insulin resistance, obesity, diabetes, vascular disease, congestive heart failure, neurological and psychiatric disorders.

Mitochondrial dysfunction plays a role in all chronic diseases. It stems from various sources: decreased mitochondrial density as shown in cell cultures from obese donors, reduced mitochondrial efficiency due to aging, and changes in mitochondrial morphology, biogenesis, or biochemical properties in heart diseases. Diverse conditions involving the neurological and cardiovascular systems, as well as severe mental disorders, share two pathophysiological processes:

1. High reactive oxygen species (ROS) production; and
2. Cumulative mitochondrial DNA (mtDNA) damage

Stress, Psychiatric Disorders and Mitochondria

This writer’s focus elucidates mitochondrial dysfunction relative to brain-mind relationships in stress and psychiatric disorders. Psychosocial and physical stressors contribute to many psychiatric conditions. Acute stress exposure of cultured neurons to either low or high glucocorticoid levels enhances mitochondrial function. On the other hand, chronic stress upregulates complex intracellular cascades, affecting metabolic integrity and mitochondrial capacities. A keynote of stress disorders is altered activity of the hypothalamic-pituitary-adrenal (HPA) axis via upregulation of corticotropin releasing hormone (CRH) in neurons of the hypothalamic paraventricular nucleus (PVN). CRH, transported to the anterior pituitary gland stimulates the synthesis of adrenocorticotropic hormone (ACTH). Once ACTH reaches systemic circulation, cortisol is released. Elevated glucocorticoids (e.g. cortisol) can impair mitochondrial function in post-traumatic stress disorder (PTSD). In animal studies, rats subjected to the stress of overcrowded cages, showed high inflammation and intestinal mitochondrial dysfunction, resulting in stress-related conditions such as irritable bowel syndrome (IBS).

High cortisol levels due to chronic stress compromise cellular energy capacity, in-
creasing neuronal vulnerability to toxic events by reducing the glucose available to CAC and ETC. Moreover, neurons with the highest firing rates, such as GABAergic interneurons (gamma-aminobutyric acid), may be deeply affected by decreased neurotransmitter release secondary to mitochondrial dysfunction. Sustained stress also induces pro-inflammatory cytokines; e.g., interleukin-1 beta [IL-1beta], IL-6 & tumor necrosis factor-alpha [TNF-alpha] in the CNS and peripherally. Cytokines activate anti- and pro-apoptotic proteins of the Bcl-2 family, and can impact mitochondrial function via intracellular signaling. Further studies need to correlate precise cytokine effects on mitochondrial function with mood disorders. Any potential drug for common psychiatric disorders, also targeting mitochondria, should be first tested in a selected psychiatric population showing mitochondrial dysfunction. Current psychotropic drugs may be treating downstream effects of more primary defects in signal transduction. Future drug therapies to alleviate anxiety and depression may be based on linking hormonal, metabolic and molecular intracellular signaling pathways.

**Thyroid hormones** (T4 and T3) play important roles in mitochondrial function. The thyroid gland controls metabolism and closely interacts with the HPA axis. Thyroxine (T4) and the catecholamines share an amino acid substrate, namely, tyrosine (from phenylalanine). Chronic stress, with its high tyrosine requirements to form catecholamines, may leave little substrate for thyroid hormone production. T4 regulates the conversion of riboflavin (B2) to flavin adenine diphosphate (FAD), an electron carrier that is alternatively oxidized and reduced. FAD is important for mitochondrial ETC, and its disruption was implicated in autism. Decreased OXPHOS in mitochondria from hypothyroid rat liver normalized after intra-peritoneal thyroxine injection. Stress reduces the conversion of T4 to the bioactive T3 hormone. T3 (triiodothyronine) enhances mitochondrial ATP production rate in the highly oxidative tissue such as liver. Moreover, T3 stimulates oxidation and regulates antioxidant enzyme activity. T3’s effects on ATP production and cell differentiation could be a major link between metabolism and development. While stress effects on the thyroid/HPA axis were not addressed in those animal studies, they are relevant to clinical practice. For hypothyroidism (even subclinical) is often seen among psychiatric patients, especially those suffering from depression.

The findings of brain mitochondrial abnormalities in individuals with neurological disorders spurred mitochondrial studies in those with psychiatric conditions. The evidence comes from electronic microscopy, imaging, gene expression, genotyping, and sequencing studies. Mitochondrial disruptions include “common deletion” and decreased gene expression in postmortem brain cells. High co-morbidity exists between conditions with impaired mitochondrial function and psychiatric disorders through decrease in neuronal plasticity, axonal transport, and neurotransmitter release. Years before their neurodegenerative disorder is manifest, over 25% of those patients receive a psychiatric diagnosis. In one study, 70% of patients with mitochondrial diseases met the criteria for the following mental disorders: major depressive disorder (MDD), bipolar disorder (BD), panic disorder, and generalized anxiety disorder (GAD).

**Mitochondrial Dysfunction in Mood Disorders, Schizophrenia, and Autism** Mitochondrial dysfunction has been associated with mood disorders, schizophrenia, and autism. Mitochondrial respiration requires the coordinated expression of two genomes with multiple subunits, a mitochondrial genome (mtDNA) and a nuclear genome. Respiratory chain disorders are genetically and clinically heterogeneous because of their biochemical complexity, showing up at birth or later in life. Those disorders lead to deficient ATP, and typically impact tissues with high energy requirements such as the CNS, which depends on oxidative metabolism. For example, children with mitochondrial encephalomyopathies may have learning disabilities (LD) in the areas of perception,
language, and memory. They may also show nonverbal cognitive impairment, compromised visuospatial abilities, and short-term memory deficits related to working memory, which reflect poor synaptic plasticity\textsuperscript{18, 24, 32}. Per recent research, children without any defined neurological condition or genetic factors may also present with learning disabilities due to mitochondrial dysfunction\textsuperscript{33}.

Mitochondrial respiration disorders significantly impact brain monoamine levels, leading to disruptions in neurotransmission dependent on serotonin, dopamine, norepinephrine, and GABA\textsuperscript{34}. Mitochondrial dysfunction is also associated with a decrease in brain-derived neurotrophic factor (BDNF) and hippocampal neurons, as well as disturbance of the HPA axis\textsuperscript{35, 36}.

**Mitochondrial dysfunction is at the forefront of hypotheses seeking to explain clinical depression.** Bipolar disorder (BD) was linked to diminished energy production and a shift towards anaerobic glycolysis. Such changes in energy metabolism may reduce cell plasticity and disrupt brain circuits linked to mood and cognitive control\textsuperscript{37, 38, 39}. Oligodendrocytes (OL) loss and malfunctions were reported in the prefrontal cortex and limbic system of patients with MDD. A certain level of functioning OLs is necessary for the dynamic control and remodeling of neuronal conduction\textsuperscript{40}. Other research showed an impairment of enzymes required for brain energy in the hippocampus of BD subjects, and upon amphetamine administration (an animal model of mania) but not in schizophrenia (SZ)\textsuperscript{41}. One animal study suggested the accumulation of mtDNA deletions in neurons causing BD-like phenotypes, and further mitochondrial research was proposed as a basis to produce new mood stabilizers\textsuperscript{42}.

Among individuals diagnosed with schizophrenia (SZ), their brains displayed abnormal mitochondrial morphology, size and density\textsuperscript{43}. Specific findings for the schizophrenic group included alterations of complex I (respiratory chain), reduction of complex IV, and age-dependent increase of mtDNA deletions in the frontal cortex and caudate nucleus\textsuperscript{25, 44}. Children with autism spectrum disorders (ASD) showed low mitochondrial enzyme function, elevated pyruvate levels, and high oxidative stress\textsuperscript{45}. In 79% of ASD cases, the etiology was not genetic but biochemical and metabolic, and included toxic exposure\textsuperscript{46}.

As a whole, the evidence from psychiatric disorders points to brain mitochondrial dysfunction and dysregulated immune response; i.e., inflammation\textsuperscript{47}. But questions remain about the varying expressions of that dysfunction, from disturbed behavior and mood (MDD) to the loss of speech (ASD), to thought disorders (SZ), or demyelination (MS)\textsuperscript{39}. Using the model for multiple sclerosis research\textsuperscript{18}, a common thread was proposed, linking myelin, inflammation, and mitochondrial function in BD, SZ, and MDD because of similar molecular signatures found in those psychiatric disorders. Gene-environment interactions determine the extent to which brain structures and functions are differentially impaired in individual patients. This, in turn, results in varying psychiatric symptoms and diagnoses\textsuperscript{49}.

**Primary Mitochondrial Diseases and Psychiatric Disorders**

Mitochondrial dysfunction, as a component of psychiatric disorders, differs from “primary mitochondrial diseases” (PMD) manifesting as psychiatric symptoms of mood disorder (depression/anxiety), cognitive decline, or psychosis. PMDs are caused by gene mutations in mtDNA or nuclear DNA, as illustrated in a review of fifty cases and one case of refractory borderline personality disorder\textsuperscript{50}. Widespread psychiatric disorders among patients with PMDs, and in those with neurodegenerative illnesses, point to the mitochondria’s role in psychiatric symptoms and their neurobiological basis. Making an accurate differential diagnosis has far-reaching implications\textsuperscript{51}. Discussion of specific PMDs goes beyond this monograph.
Since a spectrum of mitochondrial disorders are evidenced, the diagnostic process calls for multi-disciplinary, clinical and laboratory evaluations. Usually, metabolic tests are performed, there may also be a muscle biopsy, and in certain cases, genetic testing. The proposed criteria to identify mitochondrial problems are: clinical signs and symptoms, metabolic and imaging studies, and morphology. A score of 8-12 equals mitochondrial disorders, and 5-7 suggests probable mitochondrial dysfunction. The mitochondrial disease criteria are precise, facilitating the differentiation between mitochondrial and other multisystem disorders. This classification helps triage the level needed for further work with patients. In children, the application of those diagnostic criteria could precede and preempt a painful muscle biopsy.

**Metabolic Pathway Testing and Mitochondrial Function**

It is important to clarify the links between mitochondrial dysfunction, a nonspecific risk factor, and specific symptoms of psychiatric disorders. That may help define cellular markers and design molecular nutrition interventions. Those markers could also guide the creation of psychotropic drugs capable of enhancing energy metabolism and lessening oxidative stress damage. In psychiatric practice, metabolic pathway testing is increasingly used to guide therapeutic nutrition. The tests include Organic Acids from a urine sample, plasma or urinary Amino Acids, serum Lipid profiles, GI function (stool), and Toxic Exposure (blood, urine), among others. The urine Organic Acids profile assesses mitochondrial function through energy intermediates in central metabolic pathways. One section of that profile may show certain elevated analytes, to wit:

**Urinary Organic Acids Markers of Energy Cycle Dysfunction:**

- lactate excretion
- TCA cycle intermediates, such as
  - malate
  - succinate
  - 2-oxoglutarate
  - fumarate

Other elevated metabolites are:
- ethylmalonate (from butyrate, fatty acid metabolism);
- methylmalonate (B12 metabolite)
- 3-methylglutaconate (linked to aciduria)

Alternatively, one may order a combination of tests using blood and urine samples. Specific elevations point to mitochondrial dysfunction, and provide a basis for nutritional supplementation, as follows:

**Laboratory Test Markers Linked to Mitochondrial Dysfunction:**

- Lactate (lactic acid) [in blood, urine, &/or CSF due to reduced pyruvate utilization by mitochondria];
- Pyruvate [lactate and pyruvate are anaerobic breakdown products of glucose]
- Lactate/pyruvate ratio [with respiratory chain defects, the blood lactate/pyruvate increases due to changes in the mitochondrial redox state]
- Carnitine [free and total]
- Acylcarnitine panel [fatty acids attached to carnitine]
- Quantitative plasma amino acids [to measure alanine and lysine]
  - May show alanine, a product of transamination of pyruvate by alanine aminotransferase (ALT);
- BCAA (branch chain amino acids) reflect E3 deficiency [E3= subunit of the enzyme dihydrolipoamide dehydrogenase (DLD), leading to a lactic acid buildup]
- CoQ10 (ubiquinone)
- Ammonia
- Creatine kinase (CK)
- Liver enzymes: AST (aspartate aminotransferase) & ALT
- CO2 and glucose

A complete blood screening process also includes basic chemistries, and a complete blood count (CBC).

Metabolic Nutrition for Mitochondrial Therapeutics

Current trends identify nutrition as a major component of health maintenance and illness prevention [60]. Most mitochondrial therapies consist of nutritional supplementation. Biochemical individuality determines the need for nutrients, and the clinical signs of nutrient insufficiency as functional deficits develop. Genetic variations affect disease expression, such as in chronic degenerative diseases [61]. Similarly, mitochondrial dysfunction in several individuals may respond to different nutrient combinations. While varying dysfunctions may share nutrient deficits and pathway impairments, psychosocial factors shape their idiosyncratic manifestations in a person’s health. Biochemical and psychological individuality produce a symptom picture requiring proper laboratory assessment and individualized treatment.

**Nutritional support of mitochondrial function** with supplemental nutrients, vitamins, and cofactors helps in two major ways:

1. **enzyme function enhancement** for more effective energy production;
2. **antioxidant** effects, which slow, halt, or reverse progressive mitochondrial dysfunction.

In the energy cycle (CAC), the electron transport chain (ETC) is a major source and target of reactive oxygen species (ROS). ROS are linked to free radicals producing oxidative stress, often seen in psychiatric disorders. Mitochondrial-specific superoxide dismutase (SOD), along with antioxidants such as glutathione peroxidase (GSH), protect ETC from ROS damage. Antioxidant therapies based on laboratory testing of urinary Organic Acids hold promise for treating mitochondrial dysfunction in several health conditions, including mental disorders [6].

**Classification of Nutrients for Mitochondrial Support**

A two-tier classification of nutrients for mitochondrial support with daily oral dosages, provides broad guidelines for intervention [62]. Those supplements include vitamins, minerals, lipids, metabolites, cofactors, transporters, antioxidants, and enzyme inhibitors.

<table>
<thead>
<tr>
<th>Supplement</th>
<th>First Tier:</th>
<th>Dose Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>CoQ10</td>
<td></td>
<td>5-15 mg/kg</td>
</tr>
<tr>
<td>L-carnitine</td>
<td>(Carnitor, RxP)</td>
<td>Variable. Start with 30 mg/kg/qd, up to 100 mg/kg</td>
</tr>
<tr>
<td>Riboflavin</td>
<td>(B2)</td>
<td>100-400 mg</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Supplement</th>
<th>Second Tier:</th>
<th>Dose Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetyl-L-Carnitine</td>
<td></td>
<td>250-1000mg</td>
</tr>
<tr>
<td>Thiamine (B1)</td>
<td></td>
<td>50-100 mg</td>
</tr>
</tbody>
</table>
Niacin (B3)  50-100 mg
Vitamin E  200-400 IU qd to tid
Vitamin C  100-500 mg qd to tid
Lipoic Acid (ALA)  60-200 mg tid
Selenium  25-50 mcg
b-carotene  10000 IU qod to qd
Biotin  2.5-10 mg
Folic Acid  1-10 mg

Helpful Minerals, Vitamins and Substrates:

<table>
<thead>
<tr>
<th>Supplement</th>
<th>Dose Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ca, Mg, P</td>
<td>Variable</td>
</tr>
<tr>
<td>Succinate</td>
<td>6 mg</td>
</tr>
<tr>
<td>Creatine</td>
<td>5 gm bid after initial load (Adults)</td>
</tr>
<tr>
<td>Uridine</td>
<td>TBD</td>
</tr>
<tr>
<td>Citrates</td>
<td>Variable</td>
</tr>
<tr>
<td>Vitamin K3</td>
<td>5-30 mg</td>
</tr>
</tbody>
</table>

A review of clinical trials over the past decade, showed good results for many of the above nutrients in the treatment of mitochondrial dysfunction.

**Key Mitochondrial Nutrients:**

**Carnitine, CoQ10, and ATP Co-factors (B2 and B3)**

The following mitochondrial nutrients are examined here: carnitine, coenzyme Q10 (CoQ10), riboflavin (B2) and niacin (B3).

**Carnitine** is a quaternary ammonium compound (3-hydroxy-4-N-trimethylamino-butrate). It is made endogenously from lysine and methionine, primarily within muscle, liver and the kidneys, having significant effects on mental function. Carnitine abounds in meat—from “carne”; hence, the name “carnitine”—and also dairy. Several foods of plant origin (nuts, seeds, vegetables) provide some carnitine. Skeletal muscle contains 90% of the total body carnitine. It was originally named vitamin BT although it is not a vitamin.

Carnitine helps transform lipids into metabolic energ —“burning fat for fuel.” It transports long-chain acyl groups from fatty acids into the mitochondrial matrix so they can be broken down through beta oxidation to acetyl CoA, in order to obtain usable energy via CAC. Its biologically active isomer, L-carnitine, modulates the rate of fat oxidation and cell functions such as apoptosis. A carnitine deficiency impairs not only fatty acid oxidation, but also carbohydrate utilization, amino acid catabolism, and the detoxification of organic acids as well as xenobiotics.

L-carnitine was found to be effective in chronic diseases, specifically those involving the cardiovascular and endocrine systems, with controversial findings in relation to chronic renal diseases. L-carnitine and two L-carnitine esters, acetyl and propionyl L-carnitine, can improve mitochondrial function and reduce oxidative stress. Risk/benefit considerations suggest that the use of nutrients targeting mitochondria have an edge over the current pharmacological options. Future translational and clinical research can further document the ability of those nutrients to reverse pathophysiological processes. In neurology, L-carnitine is used in primary carnitine deficiency, to restore free carnitine levels and to remove toxic acyl compounds. Carnitine is available as a generic or brand-name prescription (Carnitor, by Sigma-Tau Pharmaceuticals) for oral or IV use in mitochondrial disease, effectively combined with other vitamins and cofactors.
L-carnitine facilitates fat utilization and liver detoxification, also improving cognition. But its use must be placed contextually, lest one encounters the over-dramatization created by a study linking L-carnitine to increased risk of atherosclerosis and cognitive impairment. On closer look, the real link was an increase in trimethylamine-N-oxide (TMAO)—a product of carnitine metabolism by certain strains of gut microbia. TMAO inhibited reverse cholesterol transport, reduced total bile acid, increased macrophage SRA, CD35 surface expression and foam cell formation. TMAO concentration, not L-carnitine, led to cardiovascular (CV) risk. Such data came from a type of mice at high risk for atherosclerosis. The original human data did not show a significant association between L-carnitine and atherosclerosis. Diets high in red meat, however, may lead to atherosclerosis through TMAO in those who have a predominance of certain intestinal bacteria—not every meat eater.

A similar mechanism was found in relation to lecithin and phosphatidylcholine, both essential substrates for neuronal membrane integrity. The above findings illustrate a gut-brain/mind connection, with the gut or enteric system as a prime therapeutic target-nutritionally and psychologically.

The acetylated form of L-carnitine, **acetyl-L-carnitine (ALC)**, crosses the blood-brain barrier (BBB) more effectively than carnitine. Since ALC decreases with age, it is preferred for those over forty. ALC benefits brain health and longevity. It has antioxidant properties, and is neuroprotective. ALC boosts the body’s ability to use nerve growth factor (NGF), crucial in protecting acetylcholine-producing neurons and the hippocampus. ALC repairs neuronal membrane receptors, preserves the myelin sheath, and increases acetylcholine, improving memory and learning. Furthermore, ALC reduces damaged fat molecules such as lipofuscin in the aging brain. On the skin, lipofuscin shows up as age spots. ALC also supports the heart, protects the genetic material in sperm from free radicals, and plays a role in immune defense.

There are studies on ALC’s enhancement of memory and cognition. ALC resembles the structure of acetylcholine and functions as a cholinergic neurotransmitter, having both an acetylcholine-like action and an effect on serotonergic synapses. ALC can help with age-related cognitive decline in Alzheimer’s disease as well as depression. Drugs cannot match ALC in minimizing aging effects or supporting brain health, since they do not have its breadth of functional influences.

**Co enzyme Q10 (coQ10) or ubiquinone** is a natural substance in the body, assisting with electron transfer in the respiratory chain (ETC). It is a coenzyme for many enzymes in ATP synthesis, and has antioxidant properties. There are 10 Qs in nature, but humans only synthesize Q10. Co Q10 also comes from the diet, primarily organ meats, meat, poultry and fish. Plant foods such as nuts, soy, spinach and broccoli also have a relatively high CoQ10 contents. Vegetables, fruit, eggs, and dairy products contain modest amounts.

CoQ10 synthesis entails 17 steps and several nutrients (B2, B3, B5, B12, folic acid, C, and trace elements). Unless one eats a balanced diet and has good digestion, endogenous CoQ10 may be deficient. By middle age, CoQ10 production decreases. Supplemental CoQ10 is fat-soluble, increasingly used in the treatment of OXPHOS disorders involving the cardiovascular system (CHF, hypertension, angina, stroke), and dental conditions (gingivitis). Co Q10 links to depression were the subject of a proposed clinical study that was cancelled prior to enrollment.

CoQ10 is also available as ubiquinol, a formulation with purportedly higher rate of absorption. A cost-effective alternative is to use micellized ubiquinone for full absorption. The therapeutic doses vary widely. For ubiquinol, the range is 50-600 mg po qd, and...
ubiquinone is given in a dose range of 50 mg all the way to 2400 mg po bid or tid for certain neurological degenerative disorders. A fat-soluble vitamin, CoQ10 is taken with meals. There are no known toxicities or side effects. Adverse effects include wakefulness and sleep disruption. Certain medications interfere with CoQ production, namely, beta blockers and HMG-CoA reductase inhibitors (statins), tricyclic antidepressants, phenothiazines, and butyrophenone, among others. For the older patients on anticoagulants, CoQ10 might reduce warfarin concentration. On the other side, CoQ10 reduces the effects of chemotherapy toxicity, of HIV drugs known to cause mitochondrial dysfunction, and certain psychotropic drugs3.

The writer’s experience with CoQ10 ranged from moderately positive to outstanding. Cases included integrative therapies for various mental disorders (bipolar disorder, learning disabilities, MDD, ADHD). CoQ10 also provided valuable adjunctive support in statin-treated cases of hypercholesterolemia (to offset CoQ10 depleting effects), neurological disorders (multiple sclerosis, MS), and cardiovascular conditions. Some examples of remarkable responses were two cases of bipolar disorder (males, ages 53 and 14), an adolescent with attention deficit hyperactivity disorder combined with anxiety and Tourette’s (male, age 13), one child with severe learning disabilities (male, age 8), and two individuals with MS and depression (females, ages 22 and 26). The clinical responses of most patients showing a need for CoQ supplementation—per lab tests—involved the resolution of fatigue, improved mood, positive activation, and sharper cognitive functioning. The usual dose range used was a 100 mg daily oral dose (po qd) in children and up to 300 mg in adolescents and adults. While the literature refers to daily CoQ10 doses of 50 mg or more, its systematic use in mental disorders warrants further study.

Other nutrients that help improve mitochondrial function are riboflavin (B2) and the niacinamide form of B3, both ATP cofactors as flavins and nicotine adenine dinucleotide (NAD), respectively. The dose range is 50-400 mg po qd. However, the writer favors remaining on the lower end unless otherwise indicated, and using food-derived, organic nutraceuticals whenever possible. B2 and B3 along with iodine are also very helpful adjuncts in certain cases of hypothyroidism.

B2 is an isoalloxazine. Its derived coenzymes are flavin mononucleotide (FMN) and flavin adenine dinucleotide (FAD). Powerful alkaloids and light easily destroy B2, while psyllium gum, alcohol, and antacids slow down its absorption. Food and bile salts facilitate B2 assimilation. The bioavailability of B2 is affected by certain substances that bind it, namely, copper, zinc, caffeine, theophylline, saccharin, B3, C, and tryptophan. Major food sources of B2 are organ meats, brewer’s yeast, almonds, mushrooms, and wheat germ, with egg yolks, wild rice, and many other foods containing small amounts.

For B2 or riboflavin, the dose range is 50-400 mg po qd. High doses may cause anorexia and nausea. One of the writer’s patients suffering chronically from major depressive disorder (MDD) and narcolepsy, benefited from a derivative of B2, D-ribose — a five-carbon sugar (C5H10O5). D-ribose has been used to improve sports performance by enhancing muscle energy, and in chronic fatigue syndrome (CFS), fibromyalgia, and to prevent cramps, pain and stiffness in an inherited disorder involving AMP (adenosine monophosphate) deaminase deficiency. In coronary heart disease (CAD), D-ribose is used as an intravenous (IV) application in diagnostic procedures that measure the extent of damaged heart muscle, and orally, as a beneficial supplement since it supports the heart’s energy production71. B2 is also used for nerve damage.

B3 is commonly known as niacin (nicotinic acid, vitamin PP or pellagra-preventive). Niacin is utilized to create the active cofactors nicotine adenine dinucleotide (NADH+) and its
phosphorylated form (NADPH). B3 is discussed in detail because of the ground-breaking work by Hoffer with severe mental disorders\textsuperscript{72}. As the seminal ortho-molecular psychiatrist, he reported therapeutic responses from megadoses of B3 in the schizophrenias and major affective disorders\textsuperscript{73, 74}. The best food sources are beets, brewer’s yeast, beef liver and kidney, fish, salmon, tuna, and sunflower seeds, among others. Moreover, B3 can be obtained from tryptophan containing foods, such as fowl, red meat, eggs, and dairy. Exogenously, daily oral doses above 50 mg can cause a “flush” (tingling, burning in face and chest, redness) that can be relieved by aspirin 30 minutes prior to niacin intake. Other problems with niacin are that, at the high doses required to lower cholesterol, it causes ulcers, glucose regulation problems, and elevated liver enzymes in some individuals.

A derivative of B3 without its side effects is \textit{inositol hexanicotinate (IHN)}, made of B3 and inositol. In the body, inositol nicotinate releases a form of niacin, which causes vasodilation, lowers blood lipids such as LDL, and breaks up a protein needed for blood clotting. \textbf{IHN applications} include hypercholesterolemia, hypertension, insomnia, migraines secondary to atherosclerosis, some autoimmune skin conditions (scleroderma, dermatitis, psoriasis), exfoliative glossitis involving tongue inflammation, restless leg syndrome, diabetes type 1 (facilitates decrease in insulin requirement), and several mental disorders including schizophrenia. In England, IHN is used even in conventional medical practice for various circulatory problems; e.g. intermittent claudication (legs), Raynaud’s disease (cold fingers \& toes), and cerebrovascular disease (CVD). The writer’s experience includes insomnia, fatigue, elevated blood lipids, and mental disorders. Currently, no systematic research exists with IHN. It is often recommended to supplement the whole B complex, along with active metabolites of specific B’s as needed.

\section*{Other Mitochondrial Nutrients}

Other nutrients are equally critical to improve the mitochondria and enhance mental functioning, by uplifting brain energetics on a cellular level. They are: \textit{alpha-lipoic acid} (a glutathione precursor, preferably the R-isomer), \textit{NAC} (N-acetyl-cysteine)\textsuperscript{75}, \textit{B vitamin complex} (from food sources, gut bacteria, and probiotics), \textit{vitamin C} (buffered ascorbate), \textit{E} (mixed tocopherols), \textit{L-arginine} and \textit{L-creatine}. For example, creatine showed promise as an augmentation therapy in conjunction with antidepressants for MDD\textsuperscript{75a}. Nutrients act synergistically, and so do their therapeutic effects. Vitamin combinations including CoQ10 and B vitamins are used in a “mitochondrial treatment cocktail.” Similarly, the Meyers cocktail is an intravenous (IV) application of B complex and other cofactors (e.g. Mg) that can energize the whole person.

\section*{Botanicals with Beneficial Effects on Mitochondria}

Several botanicals are associated with enhanced mitochondrial function. They have anti-inflammatory and monoamine oxidase inhibiting (MAOI) effects as well. Curcumin, a polyphenol extracted from \textit{Curcuma longa} (turmeric), improves motor and cognitive performance. It reduces oxidative damage, plaque build-up and has cholinergic effects. Curcumin may also act as an antidepressant. One randomized study of sixty subjects with MDD reported the administration of 20 mg fluoxetine \textit{po qd} and 1000 mg curcumin, individually or in combination. After six weeks, the mean change in Hamilton Depression score (HAM-D) was comparable in all three groups\textsuperscript{75b}.

\textit{Hypericum perforatum L.} (St. John’s Wort, or SJW), is a well-researched and widely used herb in the United States. Hyperforin in SJW is an effective antidepressant in varying doses. It fosters maturation of oligodendrocytes (OL) and prevents mitochondrial toxin-induced toxicity\textsuperscript{76}. SJW use must take into account an individual’s medication regimen because of herb-drug interactions, specifically hyperforin’s induction of CYP3A4 enzymes\textsuperscript{76a}.
**Rhodiola rosea** is also called “golden root” and “crenulin.” In animal studies, it increased ATP and creatine phosphate (CP) in the brain and muscle mitochondria of mice going through a forced swim test. In a human trial, Rhodiola (3% rosavins) improved several measures of mental performance: associative thinking, short-term memory, concentration, calculation, and speed of audiovisual perception. Rhodiola may also enhance ammonia re-assimilation and energy metabolism through increased ATP, RNA, protein, and amino acid synthesis. An open clinical trial showed antidepressant properties in 65% of patients\textsuperscript{77}. Rhodiola has dose-dependent effects: stimulating in low doses and calming in high ones.

**Schisandra sinensis** berry protects mitochondria, which helps explain its mental and physical energy-invigorating effects\textsuperscript{78, 79}. Schisandra relieves exhaustion, and is hepatoprotective. Its Chinese name, *wu-wei-zi* means “herb of five tastes.” Schisandra stimulates the sweet, sour, salty, bitter, and pungent receptors of the tongue which, in turn, produce stimulation of the body’s organs and systems. The usual recommended dose is 100-500 mg *po qd*. Different levels of evidence favor the use of the above nutrients and botanicals for brain mitochondria\textsuperscript{80}, and to smooth the drug-tapering process. Both Rhodiola and Schisandra are known adaptogens.

**Pharmaceutical Interventions for Neuronal Mitochondria: Animal Models**
Animal models and behavioral paradigms (e.g. motor coordination, learning, memory nociception, learned helplessness) enable researchers to assess the impact of pharmacological and nutritional interventions on mitochondria. In “learned helplessness” experiments with mice, certain antidepressants such as nortriptyline, lithium, and sertraline had neuroprotective effects. For neurodegenerative disorders, lithium rescued spinal cord mitochondria but may not have reversed motor neuron damage. Nortriptyline, a tricyclic antidepressant, slowed down degenerative processes but showed accumulated toxicity upon several months of administration.

Sertraline was thought to protect against oxidative damage and neuronal death from nitrogenous free radicals. Furthermore, fluoxetine and amitriptyline were found to increase glycogenolysis and ATP production in astrocytes *in vitro*\textsuperscript{81, 82}. An activation of the inflammatory response system characterizes depression. Antidepressants may have negative immunoregulatory effects. For example, sertraline inhibits a Th1-like pro-inflammatory cytokine (interferon-gamma or IFN-gamma) while boosting a Th2-like anti-inflammatory cytokine (interleukin or IL-10)\textsuperscript{83}. Yet the precise effects from selective serotonin reuptake inhibitors (SSRIs) on mitochondrial function remain unclear. Selegiline, a monoamine oxidase inhibitor-B (MAOI-B), improved motor performance and enhanced dopamine along with its metabolites\textsuperscript{84}.

Melatonin (N-acetyl-5-methoxytryptamine), an endogenous antioxidant, comes as an OTC (over the counter) supplement or can be obtained as a prescription drug, ramelteon (M1 and M 2 receptor agonist). It was found to slow neuronal senescence\textsuperscript{85} by lessening oxidative stress and neuronal apoptosis—the latter being linked to mitochondrial function. Melatonin possibly augments SOD activity and inhibits lipid peroxidation\textsuperscript{86}. Centrophenoxine (meclofenoxate), an antioxidant and off-label nootropic, is used in senile dementia and Alzheimer’s disease. It is made up of an ester of dimethyl-ethanolamine (DMAE) and 4-chlorophenoxyacetic acid (pCPA). It improved mice’s motor function and enhanced dopamine. It is thought to work by stimulating glucose uptake and oxygen utilization, which increase the brain’s energy metabolism\textsuperscript{84}. Centrophenoxine should be avoided by individuals with severe hypertension and seizures.

**Medication-Induced Mitochondrial Dysfunction**
Medications present a double-edged sword when benefits are pitted against side effects.
and metabolic disruptions. On one hand, an important source of mitochondrial dysfunction is made up of medications with reported mitochondrial toxicity. Among them are: acetaminophen, antiretrovirals, statins, aspirin, aminoglycoside antibiotics, erythromycin, aminoglycoside chemotherapeutics, metformin, beta-blockers, steroids, valproic acid (VPA) and several psychotropic drugs. On the other hand, the mood stabilizing agents lithium and VPA increase CNS levels of the neuroprotective protein Bcl-2. Whenever psychiatric patients show symptoms of mitochondrial dysfunction (fatigue, muscle issues, poor memory, etc), it is wise to review their history and inquire about their drug regimens. Consultation with a neurologist is indicated, in addition to a thorough physical examination. Mitochondrial disorders have multisystem manifestations.

Case reports of psychiatric aggravation triggered by neuroleptics illustrate the need for caution before prescribing. In one instance, an adolescent girl with mitochondrial disorder and depression developed new-onset psychosis and deteriorated mood with risperidone (Risperdal, 0.5 mg po bid) used to address impulsivity. She also started paroxetine (Paxil, 10 mg po qd) for depression. Within two days of risperidone discontinuation, she was free of psychotic symptoms, fatigue, psychomotor retardation, and her seizures decreased to one or two per year. She continued with the antidepressant. Marked improvement in the girl’s condition, including depression, was attributed to her taking a “mitochondrial nutrition cocktail” with carnitine (Rx Carnitor) and CoQ10. There is empirical support for supplements and enzyme cofactors (CoQ10, B complex, K), amino acids (carnitine), individualized diet, and a “vitamin cocktail” rich in antioxidants.

In vitro data showed both typical and atypical neuroleptics to inhibit mitochondrial OXPHOS. Other studies disclosed that certain neuroleptic medications (haloperidol, chlorpromazine, and thiothixene) inhibit ETC complex I enzyme activity in both rat and human brain (haloperidol, chlorpromazine, risperidone and, to a lesser extent, clozapine). Hence, those neuroleptics may exacerbate the psychiatric symptoms they are intended to treat. Neuroleptics with the least amount of mitochondrial dysfunction are olanzapine, and clozapine, followed by quetiapine. On the other hand, these agents raise the risk of metabolic syndrome, which also inhibits mitochondrial function. In addition, clozapine may produce agranulocytosis and, as a result, infections due to immunosuppression. Lack of downregulation of mitochondrial genes in the brains of individuals with schizophrenia may result from the administration of antipsychotics. OXPHOS inhibition and ETC reduction may help account for the high incidence of relapse when patients stop those medications.

Several intervening factors may help explain the contradictory findings, namely, the timing, duration, and amount of drug, along with other concurrently administered drugs. Moreover, tobacco and alcohol use, along with calorie intake are all variables impacting cellular respiration (OXPHOS). Those factors could also interact with the antipsychotics and mood stabilizers, augmenting their noxious effects. Mitochondrial dysfunction, especially in the mtDNA, interferes with higher-level functions in the brain due to its considerable energy demands. Environmental toxins also dampen mitochondrial activity. These include Bisphenol-A (BPA) used in plastics, epoxy resins, metal cans liners, cash register receipts, and food storage containers. Moreover, there are persistent organic pollutants (POPs). All those toxins may impair pancreatic beta cells, the liver and, ultimately, the brain. Air pollution and heavy metals can directly impact CNS mitochondria.

One research group systematically reviewed the positive and negative effects of several psychotropic classes (antidepressants, mood stabilizers, and antipsychotics) on different aspects of mitochondrial function. While the intent of pharmacological therapies is to alleviate suffering, they may do so at a systemic price; e.g., nutrient depletions, and the
blockage of pathways involved in energy generation and metabolism. This creates a vicious cycle of symptom formation. One way to neutralize the deleterious side effects of psychototropic drugs on mitochondrial function is to use the nutrients referenced above. Knowledge of drug-drug interactions and drug-nutrient interactions can also lead to selective prescribing and individualized supplementation. These interventions, in turn, enhance patients’ response to medication, and their long-term health.

Gastrointestinal Health and Mitochondria

Mitochondrial dysfunction interacts with digestion and GI health, increasingly recognized as a central source of physical and mental disorders. The enteric nervous system (ENS) and the enteric endocrine system (EES) mirror neurotransmitters and hormones in the CNS. Moreover, the GI tract contains the enteric immune system (EIS), making up about 70% of the body’s immunity. The friendly gut bacteria produce B complex vitamins, which are co-factors of the energy cycle. Various diseases are being linked to the prevalent strains of intestinal microflora; e.g., type 1 diabetes, leanness versus obesity (bacteroidetes vs firmicutes), hypothyroidism (Yersenia), arthritis (Klebsiella), asthma, and allergies.

Mitochondrial function affects the gut-brain connection. First, ATP is required to carry nutrients such as 5-methyltetrahydrofolate (5MTHF, active metabolite of folic acid) into the brain. This process is disrupted by autoantibody proliferation upon consumption of certain foods (e.g., gluten, cow’s milk) in sensitive individuals. A neurotransmitter cofactor, 5MTHF is also used as an augmentation agent in antidepressant therapy. Secondly, mitochondria assist with the detoxification of toxins from GI bacteria that may impair the brain. Because of the high energy requirements in GI tract and cerebrovascular endothelium, mitochondrial dysfunction may be implicated in barrier dysfunction, both in the gut and the brain.

Studies exist, indicating that intestinal dysbiosis influences brain function. GI clostridia (anaerobic, spore-forming Gram-positive rod bacteria) and other autism-associated bacteria (bacteroidetes, desulfovibrio) generate the short-chain fatty acid (SCFA) propionic acid (PPA or propanoic acid) via fermentation. PPA, in turn, inhibits mitochondrial fatty acid metabolism and function, also stimulating neuroinflammation. Carnitine-dependent pathways are thus affected. A PPA product appears elevated in the urine of patients with ASD and schizophrenia. Studies of autistic children correlate the treatment of GI clostridia with improved social interaction, eye contact, and vocalization. Furthermore, carnitine may reduce propionic acid toxicity and benefit the gut-brain connection.

Another illustration of gut-brain disruption is excessive ammonia from certain GI bacteria or incompletely digested proteins. It produces neuropsychological dysfunction when the liver fails to work properly since liver mitochondria detoxify ammonia. From the drug front, recent evidence links olanzapine to the proliferation of firmicutes, a type of bacteria that causes the gut to extract more calories from food and thus gain weight. Despite the weight loss in rats upon antibiotic administration, the authors cautioned about potential antibiotic resistance. Such treatment also raises concerns about eliminating beneficial gut bacteria that make B vitamins—a key group for CAC as well as being co-factors in neurotransmitter and CoQ10 production.

The Mind-Brain-Gut/Energy Connection

Enter the mind into the gut-brain equation: The novel field of enteric psychiatry invites us to look into the mind-brain-gut connection, “that gut feeling,” in the process of energy release through the mitochondria. Research suggests bidirectional effects: mood and feelings affect the gut’s flora and, conversely, gut microbiota influence mental states. A recent study of healthy...
women, linked the ingestion of a fermented milk product with probiotic (FMPP) for 4 weeks to positive changes in brain connectivity and responses to emotional attention tasks. This writer observed dramatic changes in energy expression among patients with mental and physical co-morbidities, from mood disorders, ASD, learning disabilities, neurological diseases, and adrenal insufficiency, to GI disorders such as irritable bowel syndrome (IBS), colitis, and intestinal permeability by using a foundational nutrition regime in tandem with psychotherapy. Having thus restored the mind-brain-gut connection, digestive competence also improved. In that context, mitochondrial support enhanced mental/emotional functioning and benefited the coordination of several body systems.

The gut has been labeled “the second brain.” Eastern cultures posit the abdomen and its organs, as the center of energy or vital force: “Hara” (Japan), “Manipura chakra” (India’s yogic tradition), “Dan tien” (Chinese medicine). Those traditions also offer meditational methods for harnessing the mind’s power to regulate, channel, and optimize energy emanating from that core—a mind-brain-gut connection. One Western attempt to integrate the gut’s immune system with the body’s energy regulators—neuroendocrine system—is the concept of a Neuroendocrine Immune Supersystem (NEI). This writer proposes a further step. Since the mind constantly interacts with NEI, the notion of a “Psycho-NEI” (PNEI) system would best unite matter and energy patterns in holistic assessment and treatment.

One case of mitochondrial disease mistaken for depression and somatoform conversions attracted significant media attention over the last couple of years. A twelve year-old girl, was so diagnosed by a psychologist who did not link the fatigue and lack of motivation to a disorder of energy metabolism. A cascade of unfortunate psychosocial developments ensued, let alone neglect of the girl’s primary medical diagnosis. The review of individual and family history contained useful leads since the girl’s sisters were being treated for mitochondrial disorders. This case highlights the need to travel back and forth from cell to psyche, in order to offer patients appropriate treatment options. Even when psychotherapy and psychosocial interventions are indicated, understanding the biological root causes of an individual’s imbalances and how they interact with their mental dilemmas, is essential for responsible and effective patient care.

**A Holistic Psychotherapeutic Matrix for Mitochondrial Support**

At present, energy-based therapies are gaining ascendancy as alternative health approaches. These include acupuncture, homeopathy, yoga therapy, massage, and other kinds of bodywork, including spinal manipulations. The investigation of how those therapies may influence mitochondrial function is timely. It is proposed here that the psychotherapeutic matrix also enhances and re-orientates energy. The “talking cure” has multilevel implications. In neuroimaging studies (fMRI), psychological parameters such as suggestion and expectation were found to modulate biological processes. Neuroscientists found that long-term change from psychotherapy correlates with functional and anatomical changes in the brain. There is also evidence suggesting that psychotherapy influences pathological processes through the modulation of specific neurochemical mechanisms. Brain plasticity, which underlies the capacity for growth, recovery, and change, depends on mitochondrial function, among other factors.

Despite advances in core neuroscience, there exist major gaps between the knowledge of neuronal plasticity and our understanding of the mind’s energy shifts. Furthermore, the interpersonal dimension is crucial since mental processes thrive or are stymied within social and cultural contexts. Psychotherapeutic communication illustrates a live energy exchange between patient and therapist with reciprocal effects. Word choices, voice inflection, tone,
facial and bodily gestures carry with them energy patterns that modify the interlocutors. One can measure those effects with psychophysiological instruments. Biofeedback-assisted psychotherapy fosters the patient’s body-mind awareness through monitoring and training respiration, heart rate variability (HRV), and other autonomic functions, plus CNS functions through brain wave feedback (neurofeedback). These methods, along with autogenics, yoga, meditation, tai chi, and hypnosis are profound catalysts of energy transformation linked to mental health improvements and physical recovery. State of the art technology such as QEEG (Quantitative Electroencephalogram), assessing brain energy at work, provides tools for building an evidence base of the “mind-mitochondrion” connection. Extrapolations and empirical links can create super highways between cell and psyche.

Research in applied psychophysiology and biofeedback has generated abundant evidence about the mind’s power to regulate body functions, especially in mitochondria-dependent organs such as the heart and the brain. ECG-EEG links were also established in relation to interpersonal factors. One longitudinal study found that the registration of cardiac energy between individuals may be enhanced in those who are more receptive to that information. When the experimenter’s ECG was used as the trigger, significant evidence of his ECG was found in the subject’s EEG (chiefly in the anterior regions) among individuals who viewed themselves in college as having been raised by loving parents. They also became healthier as adults than the subjects who were in the “low loving” group. It would be interesting to study those ECG-EEG links among veterans suffering from PTSD.

Until recently, it seemed inconceivable to modify energy-rich functions such as blood pressure, brain alertness, or temperature through mind-directed methods. Yet Eastern cultures have an age-old tradition of so doing. In a meditative state, Tibetan monks melted ice over their coats. A conscious mental focus can increase thermogenesis, which has mitochondrial input. In another instance, Buddhist monks practicing Vipassana (mindfulness meditation) showed optimal energy patterns on their EEGs. One psychologist-gastroenterologist team proved hypnosis to be effective with Irritable Bowel Syndrome (IBS). These examples demonstrate the value of mind-based methods to support mind-brain function, and mind-brain-gut connections. By enlisting the parasympathetic nervous system (PNS), those methods improve vagal signals in a context of safety (not fear or threat), modifying physiology, energy metabolism, and mental state.

From another perspective, a recent study tested the impact of glucose levels upon aggression in married couples. Glucose stemming from food intake turns into ATP, part of which contributes to brain energy. Studies show that a hypoglycemic state interferes with concentration and emotional self-control, raising the likelihood of increased irritability and spousal abuse. Low glucose levels were found to be a factor in intimate partner violence. Interventions providing individuals stable access to nutrient-dense food, are critical in stress-laden settings conducive to aggression, namely, prisons, psychiatric hospitals, and schools. Moreover, two high risk populations are dieters and diabetics. Looking ahead, the authors proposed research on glucose tolerance (how effectively glucose is broken down to produce energy) as a modulator of emotions. Since self-control requires a well-nourished, energetic brain, healthy glucose metabolism may support marital harmony.

Psychophysiologic-metabolic approaches transcend the Cartesian mind-body split, which set man apart from nature for centuries. Contemporary science and practice redefine man as a part of nature. They bring new insights into the whole person, also delving inside the power generators of the cell, i.e., the mitochondria. The human healing process restores
body-mind connections, and our mental faculties play a critical role. Through different levels of attention, we perceive, learn, and grow—or regress—as we process whatever comes in through our senses. The awareness-energy connection is our ultimate experiential reality. The mind, our “ruling sense,” dynamically watches the body reacting to the environment through neuroception. Yoga therapy (chikitsa) entails “moving” energy along the channels (chakras and nadis) and “removing” or releasing energy blocks. Movement sequences and breath with focused attention foster inner balance and improved health. Psychotherapeutic communication between therapist and patient also entails profound energy changes. It behooves us to know the process of energy production and release, and how its derailment impairs mental functions. At full circle, cell and psyche coalesce in a dynamic integration of matter and energy.

A reductionist model spotlights the genetic and biochemical bases of normal mitochondrial function. While those are important pieces of the big puzzle, the literature discloses uncertainty and incomplete answers. Moreover, epigenetic influences can encourage, alter, or mute gene expression. Hence, the profound effects of stress, negative emotions and thought patterns, disturbed bonds, violence, loss, grief, and nutrient deficiencies, especially when chronic, become prime targets to assess and heal the mind-brain/body connections energetically. Moreover, environmental toxicants and pollutants can modify that equation, and their impact on an individual’s health needs to be assessed.

Integrated functional knowledge where psychology, physiology, and nutrition meet, promotes collaboration with the specialists focusing on genes at the roots of complex molecules and metabolism. Medical psychologists thus informed can become active participants in the dialogue about mitochondria and the treatment process. They may utilize molecular nutrition and drugs as part of the treatment plan, with psychotherapeutic and experiential methods at the center. Further reflections on ways to support effectively the expression of our patients’ cellular energy for enhanced plasticity are beyond the scope of this paper, but merit future study. This is fertile ground for clinical interventions and research.

Closing Remarks and Future Directions
Ideas for a Biopsychosocial/Energy-Oriented Practice

Takeaway points from the preceding discussion are referenced below:

1) Metabolic nutrition, guided by molecular laboratory tests, offers safe and effective support for mitochondrial function within the psychotherapeutic matrix;
2) Nutrigenomics goes beyond nutritional supplements. A healthy diet and digestive competence (NEI GI function), along with mental balance are also necessary for proper nutrient utilization and metabolism—a gut-mind connection (PNEI);
3) Holistic psychotherapy draws upon the patient’s total communication, also entailin psychophysiological and nutritional assessment. As individuals reweave the strands of their lives, reframe old imprints, and build a sense of inner safety, their mode of experiencing changes. So does the mind interact with physiology and transformative cell metabolism;
4) Psychotropic drugs, now aiming to modulate neurotransmitter expression, address problems that may be secondary to basic metabolic processes in mitochondria. Novel approaches targeting mitochondria may yield pharmaceuticals that protect and enhance energy metabolism, rather than inhibiting it;
5) Medical psychologists are encouraged to add metabolic nutrition testing to their diagnostic tools, specialty nutrition to their somatic interventions (i.e. pharmacotherapy), and basic psychophysiological monitoring during sessions. In the context of collaboration with the patient’s primary care physician [PCP] or other specialists as appropriate, those modalities can lead to best clinical practices;
6) Detailed records of clinical observations can generate objective measures to test the mind-mitochondria connection within the psychotherapeutic matrix.

**Linking Mitochondria and Psyche: What is Next?**

Future steps to bridge mitochondria and psyche may yield:
1) Selected measures of mitochondrial function in relation to the psychological factors (e.g. personality, mood states, thought patterns) affecting NEI—that is PNEI;
2) Guidelines for mitochondrial support through metabolic nutrition (diet, supplements, digestive restoration) for enhanced mental and behavioral care;
3) Assessment of mitochondrial function changes from combined treatments that include psychotherapy along with somatic modalities (nutrition, psychotropic drugs);
4) Descriptions of the specific benefits from psychophysiological assessment and therapies among the interventions used to improve mitochondrial function;
5) QEEG data reflecting patterns of cognition, motor performance, mood states, and communication, which may correlate with pre- and post-psychotherapy mitochondrial function;
6) Individualized psychotherapeutic care, combining psychosocial and physiologic/metabolic methods, with the mind as key player.

**Epilogue—Minding the Mitochondria: the Chinese Way**

Over the last century, Western medicine has struggled to create a viable paradigm. The mind, a key factor in the complexities of disease expression, requires the consideration of energy. Mitochondrial models have the potential of integrating structure and energy, whose balanced interaction promotes health. The mitochondrion evolved from being a proteobacterium to becoming an “energy plant,” while the nucleus-cytosol became specialized in structure. Such design propelled the development of higher life forms, all the way to the human species. It is noteworthy that certain Asian herbal preparations were found to modulate mitochondrial energy along with tissue-specific structural functions. In such paradigm, matter and energy merge to help restore body-mind health.

A Chinese saying eloquently captures the mind’s oversight of energy, watching over the intricate communication networks in the body:

**YEN GWAN BI** (Eyes watch nose) [liver meridian à lung]
**BI GWAN SHIN** (Nose watches heart) [lung meridian à heart]
**SHIN GWAN SHEN** (Heart watches mind) [heart meridian (feelings) à mind]
**SHEN GWAN CHI** (Mind watches energy) [mind à governing vessel/energy]

To follow that,

**CHI YU DAN TIEN** (Energy develops and is stored in the gut) [energy/conception vessel]

The conception vessel and the governing vessel, respectively, rule the ying and yang principles harmonizing the whole energy system.

In conclusion, it is a long journey from cell to psyche, with the “gut feeling” as a major relay station. To flow with enteric musings, the above ideas are food for thought and assimilation, before the next burst of energy…

**References:**
5. Hroudova J, Fisar Z, & Raboch J, Mitochondrial Functions in Mood Disorders, Ch. 5, Kocabasoglu N (Ed.), *Mood Disorders*, Open Access online, 2013,101-143
57. UMDF (United Mitochondrial Disease Foundation), Diagnosis and Treatment of Mitochondrial Disease (web page).
70. National Institute of Mental Health (NIMH) Clinical Trials (Bipolar Disorder), 2011
72. Hoffer A, Dr. Hoffer’s ABC of natural nutrition for children, Quarry Press, Kingston, Ontario, Canada, 1999
73. Hoffer A, Orthomolecular Medicine for Physicians, Keats/Pivot Health, New Canaan, CT, 1997
74. Hoffer A, Orthomolecular Treatment for Schizophrenia, Keats, a division of NTC/Contemporary Publishing Group, Lincolnwood, IL., 1999
79. Pu H-J, Cao YF, He RR, Zhao ZL, Song JH, Jiang B, Huang T, Tang SH, Lu JM, & Kurihara H, Correlation between antistress and hepatoprotective effects of schisandra lignans was related with its antioxidation actions in liver cells, *Evidence-Based Compl and Altern Med*, 2012, Article ID 161062, 1-7


