

# Fatigue, Immunity, and Inflammation: Their Resolution Using Natural Medicine

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## Overview

At some point we all experience fatigue, but it usually resolves on its own and is easily explained. Sometimes it has a straightforward organic explanation, sometimes not. For many, however, such organic explanations fail to present a validated route to satisfactory resolution. As research into persistent fatigue has progressed, most clinicians comprehend that all explanatory models of the causes and mechanisms of fatigue and exhaustion proceed from the assumption that they are complex, multifactorial processes. For example, fatigue has been proposed to have biochemical, immunological, emotional, behavioral, and cognitive components, to name a few.

Fatigue is usually understood as a loss of overall energy and inability to perform even simple tasks without exertion. At the cellular level, fatigue is related to adversely altered cellular energy systems found primarily in the cellular mitochondria.

Fatigue is the most common complaint of patients seeking general medical care; between 7% and 45% of primary-care consultations involve fatigue as a major complaint.<sup>2</sup> It appears that some degree of fatigue may be identified in nearly all of the population, indicating that fatigue is not simply an individual problem; it is also a public health problem.<sup>3</sup> Fatigue can progress to the point that it causes disability comparable to that found in chronic medical patients.<sup>4,5</sup>

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At the biochemical level, fatigue is related to the metabolic energy available to tissues and cells, mainly through mitochondrial electron transport. Electron transport is directly linked to functional, intact inner mitochondrial membranes. Thus the integrity of mitochondrial membranes is critical to cell function and energy metabolism.<sup>1</sup>

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## Mechanisms of Fatigue and its Resolution

The successful management or resolution of fatigue is also important in various physical activities of relatively healthy men and women, such as work and sports performance.

Many who experience fatigue do not initially seek primary care intervention but self-treat with stimulants such as central nervous system agonists that include caffeine, herbs, and sugars. Although these provide short-term increases in energy

and perception of reduce fatigue, they have potential long-term adverse health effects.<sup>6,7</sup>

## Fatigue: Successful Intervention

Recent clinical trials using patients with chronic fatigue have shown the benefit of an oral non-central nervous system agonist: lipid replacement therapy (LRT).<sup>8</sup> Using naturally occurring glycopospholipids, cofactor nutrients, and probiotics, mitochondrial electron transport function can be restored. The result is that moderate to severe chronic fatigue can be significantly reduced in the process.<sup>9,10</sup>

Additional studies have also identified significant improvements in energy, mood, affect, and function in a healthy population following ingestion of the glycopospholipids and cofactor nutrients in a drink.<sup>11,12</sup> These additional natural agents (principally antioxidants and bacterial mediators of immune tolerance) have also shown benefits from a molecular perspective in the inhibition of immune-mediated inflammation and associated fatigue.<sup>13-16</sup>

In recent studies, using LRT and cofactor nutrients for 6 months or more has also reduced the blood levels of the amino acid homocysteine, which are related to increased risk for cardiovascular disease, stroke, cognitive loss, depression, and immune dysfunction.<sup>17</sup>

The role of glycopospholipids and other food-derived agents are attractive as safe and effective interventions in the treatment of persistent and transient fatigue. Studies have been conducted on various populations, from those with normal health and function to those undergoing complex treatments for cancer and those with persistent fatigue. These groups have shown between 30% to 40% improvement in fatigue perception and function utilising the internationally recognised Piper Fatigue Scale.<sup>18,12</sup>

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LRT is a dietary approach to replace damaged cellular lipids with undamaged (unoxidized) lipids to ensure proper function of cellular structures, such as cellular and organelle (mitochondrial) membranes. LRT can result in the cellular delivery of unoxidized, undamaged membrane glycopospholipids in order to replace damaged lipids and restore function to cellular membranes. LRT has proven to be an effective method to prevent ROS/RNS-associated changes in function and for use in the treatment of various clinical conditions.

Mitochondria are responsible for many metabolic circuits and signaling pathways. Just a few examples of these are oxidative phosphorylation, the mechanism that our cells use to generate most intracellular ATP (cellular fuel); biosynthesis of key molecules, including heme and certain steroids, as well as in many catabolic–energy relevant pathways such as the  $\beta$ -oxidation of fatty acids; and regulation of calcium homeostasis. Importantly, mitochondria are responsible for production of most of our cells' reactive oxygen species (ROS) and some reactive nitrogen species (RNS). Significant oxidative damage to mitochondrial membranes also represents the point of no return of programmed cell death pathways that culminate in apoptosis or regulated necrosis.<sup>19</sup>

### Immune Inflammation

Of clinical interest from an immunological perspective, recent studies suggest that mitochondria are significant players in the orchestration of innate immune responses via activation of a multiprotein complex called the inflammasome which results in the production and release of the pro-inflammatory cytokines IL-1 $\beta$  and IL-18.<sup>20,21</sup>

These in turn contribute to defensive and coordinated management of the bacterial organisms that reside in our digestive tract. The digestive tract is home to trillions of bacteria and this represents the site of greatest density of innate immune receptors in the body. These receptors are key mediators in the management and maintenance of immune response and tolerance. Their inappropriate activation and expression by IL-1 $\beta$  and IL-18 leads to altered innate immune hyperresponsiveness and may contribute to immune mediated inflammatory diseases as well as fatigue through the subsequent development of persistent molecular inflammation.

Damage to mitochondrial components, especially the delicate inner mitochondrial membrane, leads to the cytosolic release of toxic proteins (caspases and noncaspases) that are normally confined in the mitochondria. These released proteins then bind to specialised innate immune inflammasome activating receptors called nucleotide-binding and oligomerization domains (NODs).

These NOD receptors not only recognize intracellular pathogen-associated molecular patterns (PAMPs), but also self-generated signals known as damage-associated molecular patterns (DAMPs). Examples are extracellular ATP, uric acid, and heat shock proteins that accumulate with stress and trigger inflammasome activity. New evidence has placed inflammasomes at the center stage of complex diseases (metabolic syndrome and carcinogenesis) and physiological processes (regulation of intestinal microbial ecology) and energy management.<sup>22–28</sup>

Increased toxic metabolites and transmembrane ion leakage suppress the core ability of the mitochondria to produce ATP and alter nutrient uptake, resulting in overall reductions in energy and persistent fatigue.

Damage to mitochondrial membranes is typically due to ROS, RNS, environmental stressors, cellular aging, and mitochondriopathies. All of these factors also inhibit mitophagy – a natural process that normally limits ROS-related damage by safely removing damaged and inflammation-promoting mitochondria and mitochondrial components. This results in an inflammation-driven feed forward cycle, in which

membrane damage continues to produce ROS and RNS and DAMPs, contributing to numerous diseases and functional loss of cellular energy.

The innate immune receptors, known as pattern recognition receptors (PRRs), are stimulated by these DAMPs to induce the production of inflammatory cytokines, sustaining and promoting inflammation. These components, in turn, orchestrate the assembly of a supramolecular platform (the inflammasome), which then activates pro-inflammatory immune cytokines such as IL-1 $\beta$ , IL-18, and nuclear factor-kappa B (NF- $\kappa$ B). This process is the defining link between innate immune responses and mitochondrial functionality. Once activated, additional innate immune effects include the induction of hyperresponsive actions that occur with bacterial triggers from the gastrointestinal tract. The consequences include local inflammation, loss of mucosal barrier integrity, and fatigue.<sup>29,30</sup>

The molecular mechanisms utilized by bacteria in the gut to maintain immune homeostasis and tolerance through macrophage and dendritic cell activation can be manipulated to favor the promotion of anti-inflammatory cytokines such as IL-10 and TGF $\beta$ . The ingestion of probiotics and prebiotics can be used to mediate immune responsiveness via the promotion of regulatory T cells, dendritic cells, and low counteractivation of either T helper-mediated: Th1 and Th2 driven inflammatory responses.<sup>31,32</sup> The field of immune intervention via consumption of bacteria is over 100 years old, but has recently experienced a significant increase in interest, as the role of the bacteria in the gut is now understood to influence local and systemic illness.<sup>33</sup>

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This sequence of events places mitochondria at the crossroads of bioenergetics metabolism, cell death signaling, and the innate and adaptive immune system.

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Healthy mitochondrial function (and death) determines appropriate management of energy production, fatigue control, and innate immune-driven inflammation responsiveness. Using LRT administered as a nutritional supplement with antioxidants assures that mitochondrial membrane permeability is maintained in the optimal range, preventing oxidative membrane damage and reducing the number of mitochondrial DNA deletions. Thus LRT can be used to restore mitochondrial and other cellular membrane functions via delivery of undamaged replacement lipids to cellular organelles.<sup>34</sup>

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LRT is not just the dietary substitution of certain lipids with proposed health benefits; it is the actual replacement of damaged cellular lipids with undamaged lipids to ensure proper structure and function of cellular structures, mainly cellular and organelle membranes.<sup>12</sup>

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Inflammation is an essential immune response that enables survival during infection or injury and maintains tissue homeostasis under a variety of noxious conditions. Inflammation comes at the cost of a transient decline in local tissue function, which can in turn contribute to the pathogenesis of diseases and loss of function related to altered homeostasis. Inflammation has been described as the “common soil” of altered health and function.<sup>35</sup>



# Fatigue, Immunity, and Inflammation

Inflammation-driven fatigue is a recognized consequence of host defense, and raising immune responsiveness is an energy-dependent process that is a component of postviral and bacterial infection as well as a more recently proposed response to altered microbial composition (dysbiosis) in the human gut due to environmentally driven factors and mitochondrial damage.<sup>36,37</sup>

This suggests that alterations to the microbial balance in the digestive tract may induce loss of tolerance and subsequent increase in receptor stimulation, which in turn is amplified via mitochondrial membrane permeability, DAMP production, and inflammasome stimulation. This may then lead to “inflammasome-induced dysbiosis,” which while a relatively new area of research may provide some interesting pathophysiological connections.

## Resolution of Chronic Conditions

People with fatiguing conditions often exhibit “sickness” signs and symptoms for a variety of reasons.<sup>39</sup> One of these may be an increase in peripheral pro-inflammatory signaling. This notion is based on overwhelming evidence that pro-inflammatory cytokines are capable of inducing all the cardinal symptoms of CFS in humans.<sup>40,41</sup>

The use of selected immune-modulating probiotics along with LRT provides the cytokine milieu the opportunity to be beneficially altered through the management of mitochondrial membrane repair, DAMP reduction, and PRR-induced tolerance via changes in bacterial ratios in the gut towards ones that favor symbiosis. The activation of PRRs induces host-defense signaling pathways that culminate in the production of proinflammatory and antimicrobial molecules as well as anti-inflammatory molecules. Resolution of inflammasome-induced dysbiosis makes a considerable contribution toward improving mitochondrial fitness, just as mitochondrial fitness contributes to the healthy management of gut-mediated immune reactivity.

A central question in immunology is how the immune system discriminates between commensal and pathogenic bacteria. This problem is particularly important in the intestine, where trillions of commensal microorganisms continually challenge the immune system without eliciting a pro-inflammatory response, and where probiotics, when carefully selected by species and strain, can amplify either desired outcome.<sup>42</sup>

The results – recovery from fatigue derived from LRT and associated pro- and prebiotics, along with antioxidants – are likely due to reduced pro-inflammatory cytokines and reduced innate immune receptor hypersensitivity.

In addition to fatigue, mitochondrial dysfunction and the accumulation of damaged mitochondrial components have

also been linked to a wide variety of chronic, metabolic, and degenerative diseases; aging; and cancer.<sup>43</sup>

LRT has been successfully used in clinical studies to reduce fatigue, increase mitochondrial function, and protect cellular and mitochondrial membranes from oxidative damage.<sup>10</sup> In multiple clinical studies, fatigue was reduced 35% to 43% by oral administration of LRT and key nutrients. Even in severely fatigued patients with chronic fatigue syndrome or fibromyalgia syndrome, LRT reduced fatigue by 43.1%

In a study by Agadjayan et al., LRT (supplied as NT Factor) reduced fatigue 35.5% in aging adults and significantly improved mitochondrial function to a level that was similar to that found in young, healthy adults.<sup>44</sup>

This health-altering intersection of immunity, oxidative stress, and dysbiosis can be found in the membranes of the mitochondria residing in our cells – not only of the gastrointestinal tract but all other tissues as well. The clinical use of LRT has the potential to decrease the effects of aging on mitochondria and improve mitochondrial function in chronic diseases, diminish fatigue, and improve altered states of mucosal immunity through the participatory resolution of inflammasome-mediated dysbiosis. The improvement in terms of restitution of mucosal and immunological tolerance has potential health benefits that extend systemically.<sup>45</sup>

## Notes

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