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Fatigue, Immunity and Inflammation:– Their Resolution Using Natural Medicine.

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Michael E. Ash BSc DO ND,Prof Garth L. Nicolson Ph.D and Robert Settenari Ph.D explain the relationship between energy deficit, mitochondrial membrane quality, the immune system, inflammation and how to recover from persistent fatigue using validated natural medicine.

Overview

At some point we all experience fatigue, but it usually resolves on its own and is easily explained. Sometimes it has a straight-forward 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, behavioural and cognitive components, to name a few that contribute to overall fatigue.

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.[2] It appears that some degree of fatigue may be identified in nearly all of the population,[3] indicating that fatigue is not simply an individual problem; it is also a public health problem. Fatigue can progress to the point that it causes disability comparable to that found in chronic medical patients.[4,5]

"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.[1]"

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.[6,7]

Fatigue: Successful Intervention

Recent clinical trials using patients with chronic fatigue[8] have shown the benefit of an oral non- central nervous system agonist; Lipid Replacement Therapy (LRT ®). Using naturally occurring glycophospholipids, cofactor nutrients and probiotics mitochondrial electron transport function can been restored. The result is that moderate to severe chronic fatigue can be significantly reduced in the process.[9,10]

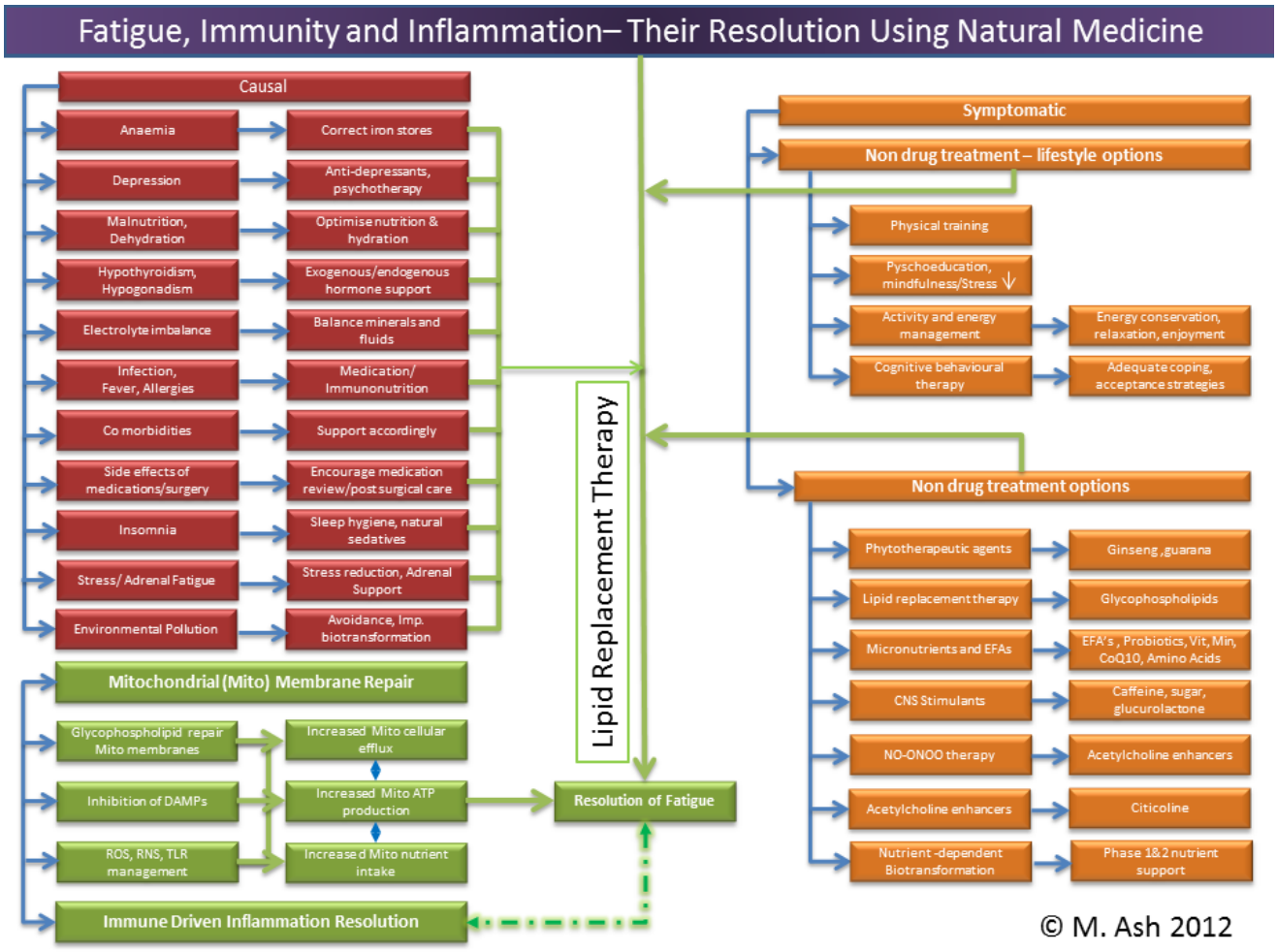
Additional studies have also identified significant improvements in energy, mood, affect and function in a healthy population following ingestion of the glycophospholipids and cofactor nutrients in a drink.[11,12] These additional natural agents (principally antioxidants and bacterial mediators of immune tolerance) have also shown benefits from a molecular perspective in the inhibition of immune mediated inflammation and associated fatigue.[13,14,15,16]

In recent studies using LRT ® and co factor 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.[17]

The role of glycophospholipids 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 30-40% improvement in fatigue perception and function utilising the internationally recognised Piper Fatigue Scale.[18,12]

"LRT® is a dietary approach to replace damaged cellular lipids with undamaged (unoxidised) lipids to ensure proper function of cellular structures, such as cellular and organelle (mitochondrial) membranes. LRT® can result in the cellular delivery of unoxidised, undamaged membrane glycophospholipids 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."

Mechanisms of Fatigue and its Resolution



There are multiple explanations, for the development and maintenance of fatigue. Reduction in mitochondrial activity both activates and is activated by the innate immune system, and this can be resolved, in part, through the restoration of mitochondrial lipid membranes and the supply of absorbable energy relevant micronutrients. These favour the restoration and optimisation of ATP and NADH production, while prebiotics and probiotics favour immunological tolerance and the restitution of inflammasome induced dysbiosis and immune driven inflammation.

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Mitochondria are responsible for many metabolic circuits and signalling pathways. Just a few examples of these include: oxidative phosphorylation, the mechanism our cells use to generate most intracellular ATP (cellular fuel); biosynthesis of key molecules including haeme and certain steroids as well as in many catabolic energy relevant pathways such as the β-oxidation of fatty acids; and regulation of calcium homeostasis. Importantly, mitochondria are responsible for production of most of our cell's 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.[19]

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-1β and IL-18.[20,21]

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-1β and IL-18 leads to altered innate immune hyper-responsiveness 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 non-caspases) that are normally confined in the mitochondria. These released proteins then bind to specialised innate immune inflammasome activating receptors called nucleotide-binding-and-oligomerisation domains (NOD's).

These NOD receptors not only recognise 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 centre stage of complex diseases (metabolic syndrome and carcinogenesis) and physiological processes (regulation of intestinal microbial ecology) and energy management.[22,23,24,25,26,27,28]

Increased toxic metabolites and trans-membrane ion leakage suppresses 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 mitochondropathies. 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 inflammatory

driven feed forward cycle, in which membrane damage continues to produce ROS and RNS and damage associated molecular patterns (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-1β, IL-18 and Nuclear Factor Kappa B (NFκβ). This process is the defining link between innate immune responses and mitochondrial functionality. Once activated, additional innate immune effects include the induction of hyper-responsive actions that occur with bacterial triggers from the gastrointestinal tract. The consequences include local inflammation, loss of mucosal barrier integrity and fatigue.[29,30]

The molecular mechanisms utilised by bacteria in our gut to maintain immune homeostasis and tolerance through macrophage and dendritic cell activation can be manipulated to favour the promotion of anti-inflammatory cytokines such as IL-10 and TGFβ. The ingestion of probiotics and prebiotics can be used to mediate immune responsiveness via the promotion of regulatory Tcells, dendritic cells and low counter activation of either T helper-mediated: Th1 and Th2 driven inflammatory responses.[31,32] 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 our gut is now understood to influence local and systemic illness.[33]

"This sequence of events places mitochondria at the cross roads of bioenergetics metabolism, cell death signalling and the innate and adaptive immune system."

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.[34]

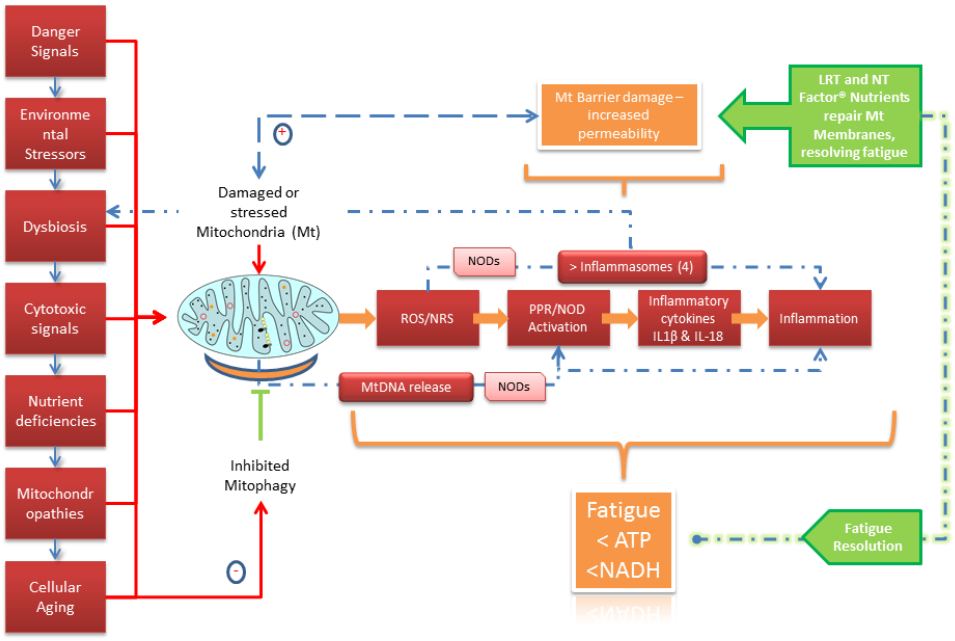
"LRT® is not just the dietary substitution of certain lipids with proposed health benefits; it is the actual replacement of damaged cellular lipids with undamaged lipids to ensure proper structure and function of cellular structures, mainly cellular and organelle membranes.[12]"

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.[35]

Inflammation driven fatigue is a recognised consequence of host defence, and raising immune responsiveness is an energy dependent process that is a component of post viral and bacterial infection as well as a more recently proposed response to altered microbial composition (dysbiosis) in the human gut due to environmental driven factors and mitochondrial damage.[36,37]

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 whilst a relatively new area of research may provide some interesting pathophysiological connections.[38]

Mitochondrial Feed Forwarding Signals That Induce Fatigue



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Danger signals including those released as DAMPs can stimulate the overproduction of ROS. ROS then promote mitochondrial permeability transition (MPT) that favours membrane leakiness, additional ROS and feed forward uncoupling. The activation of the PRR/NOD receptors and inflammasome stimulates additional mitochondrial DNA to be released. This further stimulates the inflammasomes and activating the innate immune system to respond more vigorously, including the release of proinflammatory IL-1β and IL-18. Mitophagy normally assists in the management of this process by removing ROS producing mitochondria, but DAMPs, environmental stressors, dysbiosis, cytotoxic signals, nutrient deficiencies, mitochondropathies, and cellular aging have all been associated with the suppression of mitophagy and the subsequent accumulation of damaged mitochondria. This model reflects how the activation of mitochondrial damage with altered membrane permeability leads to the production of inflammation that increases fatigue and related conditions.

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Resolution of Chronic Conditions

People with fatiguing conditions often exhibit "sickness" signs and symptoms for a variety of reasons.[39] 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.[40,41]

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 favour 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 towards 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 proinflammatory response, and where probiotics, when carefully selected by species and strain can amplify either desired outcome.[42]

The results – recovery from fatigue derived from LRT® and associated pro and pre-biotics, 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.[43]

LRT® has been successfully used in clinical studies to reduce fatigue, increase mitochondrial function and protect cellular and mitochondrial membranes from oxidative damage.10 In multiple clinical studies fatigue was reduced 35-43% 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 the study by Agadjadyan et al.[44] 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."*

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.[45]

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