23
Fatigue

Patients with fatigue suffer from constant, debilitating low energy, and tire easily during exercise or take several days to recover. Many fatigue patients struggle to think clearly as they often complain of mental fatigue or a 'brain fog'.

Many medical practitioners have suggested fatigue to have biochemical and psychosomatic components, but there is increasing evidence for the involvement of mitochondria for many aspects of the condition.

PAMPs, DAMPs and inflammation as causes of fatigue

Toll-like receptors are receptors of the innate immune system that sense the presence of microbial components. These microbial components are called PAMPs, or pathogen-associated molecular patterns. The immune system rapidly responds to PAMPs by inducing an inflammatory response and the release of reactive oxygen and nitrogen species (ROS and RNS).

Large amounts of nitric oxide are induced by toll-like receptors (via DNA gene expression) to act as another microbial agent. Excess nitric oxide and other RNS are inhibitors of the mitochondrial electron transport chain.

We can see from the above that when the innate immune system is dealing with bacterial infection, it could prove to be extremely difficult for mitochondrial energy production. Not only are mitochondria producing ROS to fight infection, but they are also themselves targets for RNS and ROS, produced by the immune system in the fight against infection.

If the fallout from fighting an infection is excessive, then our own tissue, cells and mitochondria can become damaged by the immune system's ROS and RNS 'crossfire'. If compromised, these components of our own body become DAMPs, or damage-associated molecular patterns (Morris et al. 2015a).

The innate immune system reacts to DAMPs as if they were a pathogen and can set up a vicious cycle of immune system hyperactivity. An initial inflammatory response may have been due to a pathogen triggering a toll-like receptor, but chronic inflammation may be due to DAMPs.

It is highly possible that a major factor in a patient moving from the experience of fatigue to chronic fatigue is the shift from PAMPs to DAMPs. DAMPs are likely to create even more DAMPs, unless the cycle of innate immune activation can be broken (Morris et al. 2015a).

DAMPs can undermine mitochondrial function just as well as PAMPs. Unfortunately, dysfunctional mitochondrial components can be also DAMPs in their own right (Land 2015). This is not surprising, considering the bacterial origins of mitochondria.

Failure to remove and replace worn-out mitochondria can also increase the chances of DAMPs triggering an innate immune system reaction. Mitophagy and mitochondrial quality control are therefore essential. Hence, one major cause of ongoing fatigue may be an initial inflammatory response to an invader (e.g. a bacterium) that has become chronic due to damaged mitochondria components perpetuating the inflammatory response.

Low mitochondrial quality control

Chapter 4, 'Mitochondrial Dynamics', examined the innate intelligence of mitochondrial self-management and how the organelles undergo constant quality control and renewal. Mitochondria have a shelf life which is numbered in days for most tissue. If mitochondria are not removed through mitophagy and replaced by biogenesis, then adenosine triphosphate (ATP) levels can plummet within a cell.

Lack of exercise, excess calories and insulin resistance can all play a part in undermining mitochondrial quality control (Craig 2015; Jung & Kim 2014). Once a mitochondrion is working past its 'use-by date' then it is at real risk of increasing levels of ROS such as superoxide.

It is frustrating for many people who have become out of condition through lack of exercise that they cannot simply start exercising when they realize their mistake. If their mitochondria are in poor shape, they may need a lot of biochemical support (such as resveratrol, EGCG (epigallocatechin-3-gallate), curcumin and omega-3 fatty acids, as discussed earlier) to help regenerate their mitochondria as they improve their exercise regime.

Antioxidants may quench ROS from dysfunctional mitochondria, but mitophagy and mitochondrial biogenesis are needed to really bring mitochondria back to full working condition (Liang & Kobayashi 2016).

Insulin resistance and fatigue

Underfunctioning mitochondria cannot metabolize lipids sufficiently, leading to an accumulation of lipids which will, in turn, exacerbate insulin resistance (Montgomery & Turner 2015). Therefore, insulin resistance can be both a cause and effect of mitochondrial dysfunction and fatigue.

DNA hypomethylation

Methylation of DNA plays a crucial role in switching genes on and off, and it is the most common form of epigenetic modification. Although

DNA hypomethylation is being discussed in this chapter, it is likely to be a factor in many other diseases. Patients with chronic fatigue have been found to have altered patterns of DNA methylation, with substantial hypomethylation of genes related to immune function. The overall effect of immune gene hypomethylation is to shift a person's immune system toward a more inflammatory phenotype (De Vega et al. 2014). Mitochondrial genes will also be negatively affected by hypomethylation (Singhal et al. 2015).

Inducible nitric oxide synthase (iNOS) is an inflammatory enzyme that is often found to be over-active in chronic fatigue. This over-activity results in the production of high levels of nitric oxide which can bind to, and inhibit, mitochondrial complexes (Morris & Maes 2013). Hypomethylation of an iNOS gene promoter can be one reason for iNOS over-activity (Yu & Kone 2004).

Large increases in cortisol have a negative impact on DNA methylation, particularly in a child's formative years. In many people, as we saw for autoimmune diseases, it's highly likely that later-life health issues can be traced back to early-life traumas or stresses (Nätt et al. 2015).

Fatigue sufferers often benefit from vitamin B12 injections. Could it be that vitamin B12 injections are compensating not only for B12 deficiency, but are also helping to methylate and consequently repress inflammatory genes?

Likewise, multiple sclerosis patients have found benefit from vitamin B12 injections (Wade 2002). Could high cortisol, experienced during early-life trauma, be playing a significant role in both these conditions? As stated in the previous chapter, loss of methyl groups from DNA (or DNA hypomethylation) can lead to mitochondrial dysfunction (Singhal et al. 2015).

Thyroid

Mitochondria are under thyroid hormone control. This makes absolute sense, yet the profound effect of thyroid hormones on mitochondria is not widely known. It's no wonder a hypothyroid patient feels such debilitating fatigue.

The thyroid hormone T3 can:

- stimulate oxidative phosphorylation
- activate mitochondrial biogenesis
- increase fatty acid β-oxidation.

(*Sinha et al. 2015*)

Key mitochondrial nutrients to consider in cases of fatigue

Taurine

Toll-like receptors of the innate immune system are now being considered as major players in fatigue and chronic fatigue syndrome (Gambuzza et al. 2015; Morris et al. 2015a). It therefore makes sense to find ways of reducing their negative effect on our own tissue, yet still allowing their antimicrobial activity to occur; taurine has the ability to do this. As discussed above, mitochondria play a pivotal role in toll-like receptor function.

Taurine can moderate an excessive innate immune response and yet protect against an inflammatory injury during infection (Miao et al. 2011). An example of this taurine-related positive effect on the immune system occurs in neutrophils. Neutrophils are a type of lymphocyte which contain high levels of taurine, which is used to help protect the host tissue during an immune response (Kim et al. 2010).

Taurine plays an important role in the building of the mitochondrial electron transport chain, being required to enable protein synthesis for the electron transport chain (Ito et al. 2012).

Several studies have found that taurine can help in the recovery from fatigue after exercise. Interestingly, laboratory animals deficient in taurine have great difficulty in exercising and exhibit high levels of blood lactic acid (Takahashi & Hatta 2017).

Ascorbate and α-tocopherol

In a similar way to taurine, ascorbate and α-tocopherol have been reported to reduce 'collateral damage' to our own tissue during an

innate immune response. Individually, neither nutrient is as effective; this may be due to their synergistic quality, where they can recycle each other when oxidized (Chapple et al. 2013).

Chronic fatigue patients have been found to have much lower blood levels of α-tocopherol compared to non-fatigued controls. This is thought to indicate the increased oxidative stress that occurs in fatigued patients (Miwa & Fujita 2009).

Omega-3 fatty acids

Observations of chronic fatigue patients have found that they tested for low levels of omega-3 fatty acids relative to omega-6 fatty acids. In fact, it was found that a patient's fatigue symptoms worsened as their omega-6 status increased (Morris & Maes 2014).

Like taurine, ascorbate and α-tocopherol, omega-3 fatty acids exert a moderating effect on toll-like receptors (Lalia & Lanza 2016).

Phospholipids

The phospholipid phosphatidylcholine has been shown to reduce inflammation associated with the activation of a toll-like receptor (TLR4). Conversely, the saturated fats palmitate and stearate were found to increase inflammation (Ishikado et al. 2009). Soy phosphatidylcholine was used in the study.

Soy phospholipids contain omega-6 fatty acids, which may not be ideal for patients with fatigue. A marine source of phospholipids, such as krill oil, contains omega-3 fatty acids and could be more suitable for fatigue patients. Interestingly, a study found much reduced levels of oxidative stress in krill oil-supplemented athletes who were pushed to exhaustion (Skarpańska-Stejnborn et al. 2015). An additional benefit of krill oil is that it contains the carotenoid astaxanthin. Astaxanthin has been reported to be extremely effective in protecting mitochondria from oxidative stress (Wolf et al. 2010).

'Lipid replacement' with phospholipids has been cited as a way of helping to improve energy in chronic fatigue patients. The protocol is thought to work by replacing damaged cellular and mitochondrial lipid content (Nicolson & Ellithorpe 2006). From the above research examining the actions of phosphatidylcholine in toll-like receptors,

it seems likely that immune system modulation may play a major role in the lipid replacement protocol.

Citicoline is formed from choline and cytidine. It is a precursor to phosphatidylcholine and can help prevent the loss of the mitochondrial phospholipid cardiolipin (Grieb 2014). Cardiolipin is a key component of the inner mitochondrial membrane and is attached to some of the electron transport chain complexes (Mejia et al. 2014).

Although key for mitochondrial function *inside* a mitochondrion, *outside* a mitochondrion cardiolipin acts as a DAMP (Chakraborty et al. 2017) and triggers an inflammatory response. Increased blood levels of cardiolipin and antibodies to cardiolipin are indicative of cardiolipin which has escaped the confines of the mitochondrial electron transport chain. Fatigue patients often display increased blood levels of cardiolipin and antibodies to cardiolipin (Hokama et al. 2008).

Vitamin D

Vitamin D can help reduce a heightened response of the innate immune system to PAMPs and DAMPs. Vitamin D does this via lowering the sensitivity of toll-like receptors to these inflammatory mediators. In this way, vitamin D can assist with immune system tolerance to excessive inflammatory stimuli (Ojaimi et al. 2013).

Nowhere is the need for immune tolerance more acute than in the immune system balance between mother and baby. In a similar way to immune tolerance in an individual, vitamin D assists the delicate balance of immune tolerance between mother and baby (Tamblyn et al. 2015).

Vitamin A

Vitamin A is yet another nutrient which works with toll-like receptors to help with immune tolerance (Manicassamy et al. 2009). Once again, if over-stimulated, the innate immune system will send signals to mitochondria to produce ROS instead of ATP.

The thyroid hormone T3 is an important activator of mitochondrial function. Thyroid hormones need the assistance of vitamin A, as

thyroid-responsive genes need to work side by side with the vitamin A-dependent retinoid X receptor (Sinha & Yen 2013).

Vitamin A is an essential nutrient to help maintain the integrity of the intestinal wall, and to help prevent excess intestinal permeability (Baltes et al. 2004). Therefore, vitamin A can help prevent the translocation of gut bacteria into the bloodstream, thereby reducing the chances of innate immune system activation. As discussed above, innate immune system activation is thought to be over-activated in chronic fatigue patients.

As important as vitamin A is, it is important to avoid excess vitamin A (e.g. a megadose of retinol is sometimes prescribed for acne treatment), due to its potential mitochondrial toxicity (de Oliveira 2015).

Vitamin B12

Hypomethylation of inflammatory genes is often seen in chronic fatigue patients. Chronic fatigue patients often respond well to vitamin B12 injections. It could be that the benefit that many fatigue sufferers get from vitamin B12 injections is due to improved gene methylation.

Professor Martin Pall is a world expert in the field of RNS (nitric oxide and peroxynitrite) and how RNS relates to chronic fatigue. Both nitric oxide and peroxynitrite can bind to, and inhibit, many complexes within mitochondria. Professor Pall suggests using vitamin B12 in the form of hydroxocobalamin as a nitric oxide scavenger (Pall 2001) to help improve energy levels in fatigue patients.

B12 is generally considered to be safe, but it is concerning that some recent research has discovered high B12 levels in some cancer patients (Arendt et al. 2016). This is thought to be due to metabolic changes that occur during cancer, rather than B12 driving tumour growth. Nevertheless, it is wise to exercise caution, particularly if a patient is presenting with high B12 levels without supplementation.

In cancer many protective genes are hypermethylated and switched off (Suvà 2013). So again, it's important to be cautious with B12 and folate if a patient has, or is at risk of, cancer. As a safety precaution it would be wise to order a blood test to determine blood vitamin B12 and folate status before supplementing these nutrients.

Coenzyme Q10 (CoQ10)

CoQ10 has shown promise in studies looking at supporting mental energy levels in fatigue patients (Fukuda et al. 2016). CoQ10 has also been found to reduce fatigue symptoms when combined with the supplement nicotinamide adenine dinucleotide (reduced) (NADH) (Castro-Marrero et al. 2015).

Mitoquinone (a CoQ10 analogue) acts as a mitochondrial-directed antioxidant. The design of mitoquinone allows the compound to enter a mitochondrion far more easily than CoQ10 formulated as ubiquinone or ubiquinol (Kelso et al. 2001; Smith et al. 2004; Johnson & Grant 2015). Intestinal absorption of ubiquinone and ubiquinol is not very efficient and requires high doses of both these compounds to reach mitochondria (Garrido-Maraver et al. 2014).

Mitoquinone has been reported to improve energy, mental clarity and sleep in fatigue patients. Impressively, fibromyalgia patients showed up to 33 per cent reductions in pain markers when they were supplemented with mitoquinone for six weeks (Johnson & Grant 2015).