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The Neuro-Immune Pathophysiology of Central and Peripheral Fatigue in Systemic Immune-Inflammatory and Neuro-Immune Diseases

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Abstract Many patients with systemic immune-inflammatory and neuro-inflammatory disorders, including depression, rheumatoid arthritis, systemic lupus erythematosus, Sjögren's disease, cancer, cardiovascular disorder, Parkinson's disease, multiple sclerosis, stroke, and chronic fatigue syndrome/myalgic encephalomyelitis, endure pathological levels of fatigue. The aim of this narrative review is to delineate the wide array of pathways that may underpin the incapacitating fatigue occurring in systemic and neuro-inflammatory disorders. A wide array of immune, inflammatory, oxidative and nitrosative stress (O&NS), bioenergetic, and neurophysiological abnormalities are involved in the etiopathology of these disease states and may underpin the incapacitating fatigue that accompanies these disorders. This range of abnormalities comprises: increased levels of pro-inflammatory cytokines, e.g., interleukin-1 (IL-1), IL-6, tumor necrosis factor (TNF) α and interferon (IFN) α; O&NS-induced muscle fatigue; activation of the Toll-Like Receptor Cycle through pathogen-associated (PAMPs) and damage-associated (DAMPs) molecular patterns, including heat shock proteins; altered glutaminergic and dopaminergic neurotransmission; mitochondrial dysfunctions; and O&NS-induced defects in the sodium-potassium pump. Fatigue is also associated with altered activities in specific brain regions and muscle pathology, such as reductions in maximum voluntary muscle force, downregulation of the mitochondrial biogenesis master gene peroxisome proliferator-activated receptor gamma coactivator 1-alpha, a shift to glycolysis and buildup of toxic metabolites within

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myocytes. As such, both mental and physical fatigue, which frequently accompany immune-inflammatory and neuro-inflammatory disorders, are the consequence of interactions between multiple systemic and central pathways.

Keywords Chronic fatigue syndrome · CFS · Inflammation · Oxidative and nitrosative stress · Tryptophan catabolites · Neuroprogression

Introduction

Severe intractable fatigue is endured by many people with a wide range of neuro-inflammatory, neuropsychiatric, and autoimmune disorders and cancer. Pathological fatigue is experienced by between 59 and 100 % of cancer sufferers depending on the clinical status of the disease [1]. Severe chronic fatigue is also experienced by many people with an autoimmune disease with 67 % of people with Sjögren's disease [2], up to 76 % of patients with systemic lupus erythromatosis (SLE) [3] and upwards of 70 % of people with rheumatoid arthritis [4] suffering incapacitating levels of fatigue. Upwards of 80 % of multiple sclerosis patients suffer from incapacitating fatigue [5]. Beiske and Svensson reported that between 37 and 57 % of patients with Parkinson's disease experience incapacitating fatigue [6]. Winward et al. reported data which strongly indicates that fatigue in stroke victims is a direct consequence of the cerebral infarct and not merely a consequence of increased effort during rehabilitation [7]. Severe fatigue was experienced by 87 % of people following major stroke 56 % of people following minor stroke and 29 % of people following a TIA [7]. Fatigue is commonplace in people following a myocardial infarction with almost 100 % of patients reporting debilitating levels of exhaustion. Interestingly, many patients reported severe fatigue without any concomitant signs of depression [8]. Numerous studies report a high co-morbidity between severe fatigue and major depression [9]. Fatigue is a hallmark symptom of depression in bipolar disorder, where so-called atypical depression is disproportionally present; this includes fatigue, hypersomnia, and carbohydrate craving [10]. Severe fatigue is also commonplace in people with chronic obstructive pulmonary disease and mild traumatic brain injury with 38 and 39 % of patients, respectively, suffering the fatigue symptom [11, 12]. In the case of inflammatory bowel disease, 40 % of patients suffer severe intractable fatigue even when in remission [13]. Pathological fatigue is also a mandatory element in affording a diagnosis of idiopathic chronic fatigue, chronic fatigue syndrome, and myalgic encephalomyelitis [5].

Mental fatigue involving an impaired capacity for concentration, learning, attention, and disturbance of short-term memory is commonly observed in neurodegenerative and neuro-inflammatory diseases, such as multiple sclerosis, and Alzheimer's and Parkinson's disease [14–19]. Mental fatigue presents as an impaired ability to take in and subsequently process information over any given time period. Mental exhaustion is generally precipitated during prolonged incessant cognitive tasks. Symptoms of mental exhaustion are usually absent or trivial when a patient is relatively relaxed and stress free. Mental fatigue predominates following sleep deprivation. Patients with mental fatigue often report extreme sensitivity to noise and light and severe headaches [20].

Activated immune-inflammatory pathways, oxidative and nitrosative stress (O&NS), mitochondrial dysfunctions, and brain metabolic disorders are involved in the pathophysiology of severe fatigue [21]. A chronically activated peripheral or central immune system is a feature of autoimmune disorders, such as Sjögren's disease, systemic lupus erythematosus and rheumatoid arthritis, and neuro-inflammatory diseases, such as Parkinson's disease, multiple sclerosis and stroke [22, 9]. It may be no coincidence that elevated levels of oxidative stress are found in patients with systemic lupus erythematosus [23], Sjögren's disease [24], rheumatoid arthritis [25], Parkinson's disease [26], multiple sclerosis [5], stroke [27], cancer [28], depression [29], and bipolar disorder [30]. Mitochondrial dysfunction is also a common finding in all these disease states [23, 24, 31, 32, 21]. Elevated levels of O&NS, mitochondrial dysfunction and a chronically activated immune system, together with neuroimaging abnormalities, are found in many individuals with a diagnosis of CFS [5, 21].

This review aims to examine the various pathways capable of generating intractable fatigue of peripheral or central origin. We will review that central fatigue does not only result from elevated levels of pro-inflammatory cytokines, increased O&NS and mitochondrial dysfunctions, but also pathological changes in glutaminergic and dopaminergic neurotransmission, functional or structural abnormalities in brain regions, including the prefrontal cortex and the basal ganglia. We will review that peripheral fatigue can stem from the breakdown of the homeostatic relationship between cortical and spinal neuron activity in striated muscle and increased patterns of gene expression in exercising muscle with or without the buildup of toxic metabolites within myocytes.

Immune-inflammatory and O&NS pathways leading to fatigue

Immune-inflammatory pathways and incapacitating fatigue

It has been proposed that fatigue stems in part from immune dysregulations and consequent cytokine abnormities in diseases such as Parkinson's disease [33], multiple sclerosis [34], fibromyalgia [35], cancer [36], CFS [37, 38], and

depression [39]. There is also strong evidence that cytokines make a considerable contribution to the development of stroke associated fatigue and neuro-inflammation [40, 41]. For example, high levels of interleukin-1 (IL-1) β, a pro-inflammatory cytokine, and depressed levels of IL1-receptor antagonist (IL-1RA), which inhibits IL-1 signaling, are robust predictors of the development of chronic fatigue after acute ischemic stroke supporting the role of chronic inflammation in the genesis and possible long-term maintenance of post stroke fatigue [42].

Several authors have implicated increased levels of pro-inflammatory cytokines in the generation of fatigue in ill and healthy individuals. Chronically sick patients with high underlying levels of inflammation experience markedly greater rates of fatigue than age-sex matched population norms [43, 44]. This association may be explained by invoking the concept of cytokine-induced illness behavior and the effects of IL-1, IL-6, IL-2, and interferon-(IFN) α, acting in the brain to induce symptoms such as fatigue, anhedonia, loss of appetite, weight loss, sleepiness, etc. [45]. There is now overwhelming evidence that the acute response to pathogen is mediated via the actions of pro-inflammatory cytokines, including IL-1β, IL-6, and TNFα, [46–50]. Pro-inflammatory cytokines in the systemic circulation are actively transported to the brain by transporters on endothelial cells or by via diffusion through relatively permeability areas of the blood-brain barrier [51]. Signals relating to systemic immune-inflammatory responses also reach the nuclei of the solitary tract and the caudal medulla [51–53] through afferent vagal signals induced by the presence of pro-inflammatory cytokines in lymph nodes and the spleen. Ultimately, signals from ascending neural pathways conveying information regarding the status of peripheral activation of immune-inflammatory pathways induces the 'danger pathway' in the caudal brainstem, leading to attenuated arousal mediated by the hypothalamus [54]. Effects of TNFα, IL-1β, and IL-6 not only result in the activation of microglia and astrocytes inducing neuro-inflammation [55, 56], but also inhibit energy-consuming locomotor, and neurocognitive processes ensuring that energy is diverted from tissues, including peripheral organs and the brain, to be mobilized to counteract pathogen-induced pathology. The energy conserved by this cytokine-regulated process initiates and maintains pyrexia which enhances the performance of immune cells and inhibits viral replication [57–59]. Neuro-inflammation and microglial activation may also be provoked by the presence of lipopolysaccharide (LPS) from gam negative bacteria in the systemic circulation [46]. We recently reviewed the role of increased LPS following increased bacterial translocation in the initiation of fatigue and other illness symptoms [55]. Many of the symptoms associated with the sickness response are conserved by evolution with the express purpose of redirecting and conserving vital energy produced by mitochondria to meet the high energetic requirements of the immune response [57, 60].

Significant evidence that inflammatory cytokines can cause a stereotypical symptom complex dominated by severe fatigue derives from monitoring the effects of exogenous administration of IFNα. IFNα is a cytokine which is a key player in the innate response displaying both antiviral and antiproliferative capabilities and is thus often used to treat infectious diseases and cancer [61–63]. IFNα has often been detected in the CSF of patients suffering from a number of different infectious diseases such viral and bacterial meningitis [64]. The presence of elevated levels of this cytokine in the CSF of people with systemic lupus erythematosus and Aicardi-Goutieres syndrome is perhaps more surprising. It is thus worth noting that elevated concentrations of IFNα in the blood and CSF of patients diagnosed with these conditions is associated with diffuse chronic neuropathology [65, 66]. IFN α administration results in the development of severe fatigue together with psychomotor retardation [67–69]. It is worthy of note that these INFα-induced symptoms are refractory to therapy with selective serotonin reuptake inhibitors [70, 71]. This phenomenon is in agreement with observations in cancer patients, treated with inflammation and fatigue inducing chemotherapy, whose fatigue is also unresponsive to selective serotonin reuptake inhibitors [72, 73].

There is now considerable evidence implicating neuro-inflammation and the accompanying disruption of the blood-brain barrier (BBB) in the genesis of mental fatigue [74]. The relationship between the development of neuro-inflammation and the presence of elevated pro-inflammatory cytokines in the periphery is well documented [55, 56]. BBB disruption is observed quite early in neuro-inflammation, and parallels the release of pro-inflammatory cytokines [75–77]. Mechanisms underpinning BBB disruption in these conditions may involve effects of pro-inflammatory cytokines on endothelial cell tight junctions [56, 78, 79]. Cytokines, including TNFα and IL-1β, play a key role in the maintenance of neuronal functions and modulate neurotransmitter systems and neurocircuits in the brain, thereby resulting in behavior changes [80, 81]. Under normal physiologic conditions, these cytokines are involved in many indispensable brain processes such as long-term potentiation, synaptic plasticity, and neurogenesis [81].

Peripheral administration of IFN α leads to an increase in central IFN α levels, which consequently induce immune-inflammatory responses typified by elevations in IL-6 and monocyte chemoattractant protein-1 (MCP-1) [82–84], which are responsible for summoning monocytes into the CNS [85, 86]. The induction of MCP-1 is the main mechanism by which IFNα evokes inflammatory responses in the CNS [87]. MCP-1 elevations together with accompanied elevations of IL-6 have the capacity to prime microglia in the brain subsequent to administration of several different inflammatory stimuli to the CNS, including LPS [88]. It also seems worthy of note that loss of BBB integrity often noted during IFNα therapy may be facilitated by MCP-1, offering a potential mechanism by which a temporary but massive increase in IFNα levels following a prolonged viral infection may lead to chronic neuropathology. In fact, numerous studies have revealed that

prolonged elevation of MCP-1 levels can markedly increase the permeability of the BBB via effects on the C-C motif chemokine receptor-2 receptor [85].

Microglia, astrocytes, and plasmacytoid dendritic cells [PDCs], which are normally resident within the meninges but are recruited to the parenchymal tissue of the brain following immune activation, have the capacity to produce IFNα [89, 90]. It has been demonstrated that IFNα-stimulated microglia in vitro generate IL-1, superoxide production and elevated levels of oxidative stress [91], suggesting that IFNα powers neuro-inflammation induced by microglia [92].

Although IFNα levels in the brain during exogenous administration are low in comparison to levels of MCP-1 and IL-6 [93], the amount detected is probably the result of the administered IFNα [82, 84]. The CNS responses in IFNα-treated patients indicate that IFNα likely enters the brain via leaky regions in the BBB and or provokes cells at the BBB to produce IFNα on the CNS side of the BBB. The latter explanation appears particularly attractive as IFNα has the capacity to upregulate numerous immune genes in endothelial cells such as those forming an integral part of the BBB. These include genes for Toll-Like Receptor (TLR) 3 and IFN regulatory factor 7 (IFR7), which play indispensable roles in IFNα production following numerous immunological stimuli such as a virus infection [94–96]. All in all, the weight of evidence demonstrates that IFNα has the capability of accessing and likely entering the brain [82, 97] despite the apparent lack of a saturable transport system in the BBB [98].

Oxidative and nitrosative stress pathways and incapacitating fatigue

A review involving patients with cancer or chemotherapy-induced fatigue referenced four studies where oxidative stress was held to be the cause of severe fatigue experienced by patients in those studies [99]. Elevated O&NS is also causatively implicated in the development of severe central or "systemic" fatigue [100–103]. A recent review highlighted seven studies where authors cited a significant positive association between oxidative stress and severity of fatigue in patients diagnosed with CFS [5]. Oxidative stress is dramatically elevated in patients with CFS compared to healthy controls during the conduct and aftermath of exercise [104, 105].

There is now ample evidence that rapid and massive increases in ROS production in the immediate aftermath of acute ischemic stroke overwhelm cellular antioxidant defenses, leading to further tissue damage in the penumbra [106]. These radicals can cause severe damage to lipids, proteins, DNA, and cell membranes leading to further neuronal loss by apoptosis or necrotic cell death [106, 107]. Furthermore, the rapid restoration of blood flow massively increases mitochondrial ROS production resulting in cellular damage and death characteristic of reperfusion injury [107, 27]. Wang et al. demonstrated a positive and significant correlation between elevated biomarkers of O&NS and objective measures of disease activity in systemic lupus erythematosus [108]. The existence of elevated O&NS also been repeatedly demonstrated in patients afforded a diagnosis of Sjögrens syndrome [24, 109], rheumatoid arthritis [110, 111, 112], Parkinson's disease, and multiple sclerosis [5].

Numerous studies have demonstrated increased levels of ROS and RNS during exercise [113, 114] and the role of these radical species as essential signaling molecules in normal muscle function is well established [115, 116]. Skeletal muscles generate ROS and RNS at elevated rates during contraction [113, 114]. O&NS accelerates the development of muscle fatigue [117–119], weakness, and overall muscle dysfunction [120–122]. In similar vein, increased levels of RNS secondary to iNOS production cause muscle weakness and dysfunction in inflammatory pathways [120–122].

Administration of *N*-acetyl cysteine, an antioxidant, suppresses fatigue originating during activation of the tibialis anterior muscle, supporting the view that ROS scavenging plays a role in human muscle fatigue [123, 124]. Numerous studies have shown a role of ROS and ROS scavenging in muscle fatigue and force modulation [125, 126]. Interestingly, there is additional evidence that blockade of RNS can attenuate muscle fatigue [127, 128].

The adverse effects of increased O&NS on muscle cell function may be induced via a number of different mechanisms, which include dysregulation of the sarcoplasmic reticulum (SR), calcium release channel [129], depression of SR dependent ATPase activity [130], diminishing the use of oxygen by mitochondria overall and suppressing the activity of cytochrome c oxidase [21, 131, 132]. NO donors may cause a wide range of adverse reactions including decreasing the activity of cytochrome c oxidase [131], the disruption of calcium regulation [133], depression of contractile force [134] and diminished mitochondrial oxygen utilization [131], which conspire to accelerate the development of fatigue [117–119].

ROS that are generated by TNFα stimulation inhibit myogenesis via NF-κB-related mechanisms [135, 136]. NF-κB signaling appears to play an auxiliary role in atrophy of skeletal muscle induced by ROS [137]. NF-κB and ROS negatively impact skeletal muscle differentiation [138, 139]. Myoblast differentiation into myotubes is of paramount importance for muscle repair, regeneration, and function [140]. O&NS is known to at least partly underpin the pathology in a wide range of muscular pathologies characterized by abnormal differentiation [138, 141, 142].

The toll-like receptor radical cycle and incapacitating fatigue

Engagement of TLRs by pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs) leads to the initiation of the innate immune response

[143]. Activation of the TLR2/4 complex induces the expression of intracellular signaling networks, such as NF-κB and mitogen-activated protein kinases (MAPK) with subsequent upregulation of pro-inflammatory cytokines, ROS and RNS. [143–145].

Classical DAMPS capable of triggering pattern recognition receptors and the subsequent activation of the immune response include high-mobility group protein B1 (HMGB1), ATP, degraded hyaluronan, heat shock proteins, substance P, uric acid, the S100 proteins and damaged or degraded DNA [146]. HMGB1 and the S100 family of proteins are released following necrotic cell death [147, 148]. HMGB1 activates TLR2 and TLR4 [149, 150], while S100 DAMPS are capable of upregulating TLR4 receptor activity directly [151] or indirectly [147]. Increased levels of ROS and RNS produced by TLR activation can attack unsaturated membrane fatty acids and other cellular molecules generating a range of damaged molecules, including oxidized phospholipids, 4-hydroxynonenal (4-HNE), malondialdehyde (MDA), oxidized low density lipoprotein, and nitroso-protein adducts, protein carbonyls and oxidized and degraded DNA [152, 153]. Alpha beta ketones and aldehydes, protein carbonyls, and other products of lipid peroxidation and protein oxidation also act as DAMPs [152, 154].

These damaged molecules in turn function as redox-derived DAMPs exacerbating TLR2 and/or TLR4 activity, thereby driving increased synthesis of pro-inflammatory cytokines, ROS, and RNS [143]. 4-HNE and MDA are particularly aggressive entities, which attack proteins leading to the creation of reactive carbonyl adducts [155, 156], which, in turn, behave as potent redox-derived DAMPS [154]. Degraded mitochondrial DNA is also known to act as a DAMP and activate TLR-2 and TLR-4 receptors [157, 158]. The TLR radical cycle once further activated by redox-derived DAMPs may rapidly become self-sustaining and self-amplifying and may well underlie the excessive levels of nitro-oxidative stress and chronic immune activation seen in patients with neuro-inflammatory, neurodegenerative and autoimmune diseases [143].

Many patients with a diagnosis of CFS display increased IgM/IgA responses directed against LPS from gram-negative enterobacteria [45], which are known to act as PAMPS capable of activating TLR2/4. Numerous studies have also reported antibodies to an almost bewildering array of pathogens in people with CFS at levels significantly higher than in control subjects [5]. The pathogens that may mediate immune responses via engagement of TLR2/4 include Human Parvovirus 19 [159], Coxsackievirus B [160], HHV-6 [161], *Coxiella burnetii* [162], *Borrelia burgdorferi* [163], and *Campylobacter* species [164]. Activated TLR2/4 complexes are found in many inflammatory and neuro-immune disorders. Gow et al. detected activated TLR4 in patients they described as having "post infectious CFS" [165]. Elevated TLR4 signaling was also detected in a cohort of patients with CFS by Light et al. [166]. TLR4 receptors are also upregulated in the brain and peripheral immune system in patients with multiple sclerosis [167–169]. The same is true of patients with Parkinson's disease [170] and depression [171]. Upregulated TLR4 signaling is also commonly observed in patients with autoimmune diseases and as a phenomenon observed in for example systemic lupus erythematosus [172], Sjögren's disease [173], and rheumatoid arthritis [174]. Finally, TLR4 is upregulated in people with cerebrovascular disease and chronically following a major or minor infarct [175]. All in all, an activated TLR radical cycle stimulated by PAMPs and classical and redox-derived DAMPs is associated with chronic immune-inflammatory and O&NS processes which in turn play a pathogenetic role in chronic immune-inflammatory disease and in the disabling fatigue that accompanies these diseases and processes.

IO&NS pathways, neurotransmitters, and fatigue

IO&NS pathways, glutamate metabolism, and fatigue

Another pathway through which pro-inflammatory cytokines may induce chronic fatigue is through effects on glutamate neurotransmission. One major theory is that elevated levels of pro-inflammatory cytokines underpin the pathophysiology of mental fatigue as a result of their capacity to impair glutamate clearance by astrocytes and their widespread deleterious effects on astroglial cells and, consequently, the supply of metabolites to neurons leading to the attenuation of glutamate transmission [74].

Glutamate neurotransmission is vitally important in information processing within the CNS [76] and for long-term potential formation and memory formation [176]. In the brain, extracellular glutamate has to be maintained within narrow limits to ensure a high-precision signal during normal glutamate neurotransmission [177] and also, to prevent glutamate induced neuron excitotoxicity. Glutamate clearance is enabled by sodium (Na+)-dependent uptake transporters, e.g., the glutamate aspartate transporter (GLAST) and glutamate transporter 1 (GLT-1). Both are found at highest concentrations on astrocytes enwrapping synapses of neurons bearing glutamate [178]. Astrocytes play the lead role in maintaining extracellular glutamate levels within physiological norms via glutamate transporters on their surface and relaying calcium ions signals within local and remote neural networks [179, 180]. There is now overwhelming evidence that the optimal performance of these glial cells regulating extracellular glutamate levels underpins information processing, including memory formation and retrieval [181, 182].

Pro-inflammatory cytokines, such as TNFα, IL-1β, and IL-6 impair astroglial glutamate uptake leading to the

excessive levels of extracellular glutamate thought to be the ultimate source of mental fatigue. A synthesis of the data from several studies indicates that TNFα inhibits astroglial reuptake of glutamate via the promotion of glutamate induced oxidative stress leading to reduced levels of astrocytic expression and function [183, 184]. Elevated levels of IL-1β and IL-6 appear to inhibit glutamate reuptake by astrocytes via a very similar if not identical mechanism [185, 186]. Lowered astroglial glutamate uptake capacity decreases neuronal uptake of astroglial glucose and metabolic substrates [187, 188].

Adverse consequences on information processing also flow from the disruption of the blood-brain barrier which is an early event in the development of neuro-inflammation [189]. While glutamate transporters on astrocytes and neurons (EAAT 1, EAAT 2, and EAAT 3) play a vital role in keeping glutamate levels within the brain, low glutamate receptors on the abluminal membranes of the BBB also make a major contribution to this endeavor by promoting the removal of glutamate from the brain while simultaneously preventing entry from the systemic circulation [190, 191]. Neuro-inflammation reduces astrocyte gap junction activity impairing the regulation of glutaminergic neurotransmission [192]. Neuro-inflammation also leads to the downregulation of astrocytic glutamate transporter expression via excess levels of glutamate secreted by activated microglia and hence leads to elevated levels of glutamate [193].

Another mechanism exists involving the effects of tryptophan catabolites (TRYCATs), such as kynurenine and quinolinic acid, which have multiple effects on glutamate neurotransmission in the brain. Indoleamine 2,3 dioxygenase (IDO) is activated by pro-inflammatory cytokines, including IFNγ, IL-1, IL-6, and TNFα, acting alone or together or in combination with NF-κB and p38 MAPK [194–196]. IDO is synthesized in several cell types which include microglia and macrophages and catalyses the breakdown of tryptophan to TRYCATs locally in the CNS or incorporated from the periphery [197, 198]. Kynurenine is further catabolized into quinolinic acid in microglia and kynurenic acid in astrocytes. These TRYCATs are both elevated in the CSF of IFNα-treated patients [199]. Elevated levels of quinolinic acid not only contribute to the generation of increased oxidative stress, but an also activate the *N*-methyl-D-aspartate (NMDA) receptor causing glutamate release [199, 200]. Glutamate release together with oxidative stress can cause excitotoxicity and therefore many authors have implicated excessive levels of quinolinic acid as a contributor to the development of several neurodegenerative illnesses including Huntington's and Alzheimer's disease [199, 201, 202]. Kynurenic acid, however, inhibits glutamate release, and acts as an a-amino-3-hydroxy-5-methyl-4-isoxazolepropionicacid (AMPA) and NMDA receptor antagonist [203].

Finally, cytokines may attenuate the expression of glutamate transporters and increase glutamate release [204, 205]. Once released, glutamate may target extrasynaptic NMDA receptors causing a lowered production of neurotrophic factors, e.g., brain-derived neurotrophic factor [206, 207]. There is now considerable evidence that elevated levels of glutamate and subsequent glutamate excitotoxicity is a source of neuropathy or neurodegeneration in Alzheimer's disease [208], Parkinson's disease [209], amyotrophic lateral sclerosis [210], Huntington's disease [211], stroke [210], multiple sclerosis [212, 213], depression [214–216], and other neuropsychiatric disorders [217]. A grim illustration of the neurotoxic potential of TRYCATS can be seen in data appertaining to their production in Alzheimer's disease and the aftermath of ischaemic stroke [218, 219]. As described above, TRYCATs cause increased glutamate levels and thus could be associated with the mental fatigue that accompanies TRYCAT-related diseases. Figure 1 shows the relationships between the TRYCAT pathway, glutamate, EATT and dopamine (see also next section).

IO&NS pathways, dopamine metabolism, and fatigue

The weight of evidence now strongly suggests that pro-inflammatory cytokines may target dopamine in the basal ganglia [80, 220]. These actions of pro-inflammatory cytokines on dopamine neurotransmission may be particularly important, relevant to the development of fatigue [92]. Dopamine plays a key role in motivation, drive, psychomotor function, and the promotion of goal-directed activity, and hence in energy and mood regulation [221, 222].

Cytokines have the capacity to decrease dopamine metabolism in the basal ganglia by several different mechanisms which include impairing its synthesis and packaging as well as stimulating its reuptake. Several enzymes which are indispensable in the synthesis of dopamine from tyrosine require the presence of an essential highly redox sensitive coenzyme called tetrahydrobiopterin (BH4). This enzyme may be irreversibly oxidized and hence inactivated in an environment of elevated oxidative stress generated directly or indirectly by pro-inflammatory cytokines [80, 223].

The optimal functioning of dopaminergic neurotransmission is dependent on the packaging of dopamine into vesicles before its release via the vesicular monoamine receptor-2 (VMAT-2). Without this process, dopamine is highly liable to auto-oxidation with the resultant production of a range of neurotoxins and ROS [224]. Decreased VMAT-2 activity can indeed lead to auto-oxidation and ROS production [224, 225]. There is some evidence that elevated levels of IL-1β and TNFα can reduce the activity of vesicular monoamine receptor [226]. The weight of evidence indicates that activation of the p38 MAPK pathway by pro-inflammatory cytokines influences the activity

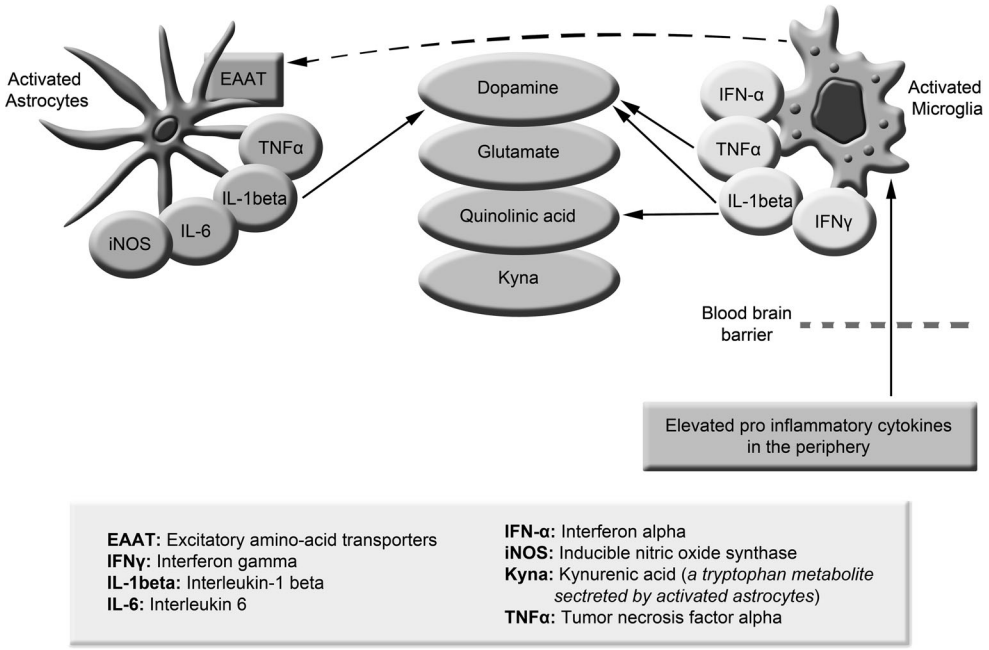


Fig. 1 Microglia and astrocytes become activated by signals relaying the presence of increased concentrations of pro-inflammatory cytokines (PICs) in the systemic circulation and the spleen which reach the brain by a variety of routes. Once activated, glial cells produce pro-inflammatory cytokines (PICs) and oxidative and nitrosative stress (O&Ns). Interferon (*IFN*) α and a range of other neurotoxic and neuromodulatory substances such as the tryptophan catabolites (TRYCATs), including quinolinic acid, kynurenine, and kynurenic acid (*kyna*). PICs and TRYCATs conspire to inhibit the reuptake of glutamate. An environment of glutamate excitotoxicity and a decrease in dopamine levels are crucial factors in the genesis of cognitive and sensory fatigue. IFNα and activated astrocytes result in impaired glucose metabolism and delivery of oxygen and energy to areas of elevated neural activity. These abnormalities associate with the development of severe intractable fatigue

of dopamine transporters leading to an increased reuptake of dopamine [227–229]. Finally, the release of dopamine is partly mediated via glutamatergic systems and hence increased kynurenine acid may inhibit dopamine metabolism [199].

A further pathway whereby dopamine influences energy is its direct effects on mitochondrial function. Dopamine has direct effects on mitochondrial function, causing mitochondrial permeability pore transition, reducing oxygen consumption, and uncoupling [230]. In Parkinson's, dysregulated dopamine transmission is linked to mitochondrial dysfunction. Dopamine has direct effects on mitochondrial complex I in particular [231]. Agents driving dopamine, prototypically amphetamines, cause mitochondrial dysfunction [232].

Decreased dopamine is one of the accepted causes of the severe incapacitating fatigue in people suffering from major depression as discussed previously. The relationship between impaired dopamine production and the production of the severe physical fatigue experienced by many people with Parkinson's disease however was a matter of some considerable controversy until 2003. In that year, Lin and others presented the results of an elegant double blind study demonstrating conclusively that physical fatigue suffered by Parkinson's disease patients was indeed mediated largely by impaired dopamine production [233].

IO&NS pathways, mitochondria dysfunction, and fatigue

ATP and the electron transport chain

Central and peripheral fatigue often with concomitant exercise intolerance, are common symptoms of mitochondrial diseases [234, 235]. Mitochondrial diseases may be classified as syndromic or non syndromic [21] and the bewildering array of symptoms presented by people with mitochondrial disease is ultimately due to impaired oxidative phosphorylation and generation of ATP caused by mutations in mitochondrial or nuclear DNA [21, 234, 236]. While congenital and acquired mutations are both known to cause mitochondrial disease, there is a growing awareness that secondary mitochondrial dysfunction can occur as a result of chronic O&NS and elevation of pro-inflammatory cytokines [21, 237]. Such dysfunction likely impairs oxidative phosphorylation and ATP production via a number of different mechanisms [21]. Excessive levels of nitric oxide inhibit the activity of enzymes which form complex I and complex IV of the electron transport chain [238–240]. These enzymes are also inhibited, probably irreversibly, by another RNS namely peroxinitrite [21, 240]. Inhibition of these enzymes not only blocks the production of ATP but leads to a massive increase in ROS generation by mitochondria, due to incomplete oxygen reduction, and this in turn begets more RNS and more damage to the electron

transport chain and other essential mitochondrial components leading to a spiral of increasing bioenergetic decline [21]. O&NS also drives a shift towards glycolysis rather than oxidative energy generation [237].

IO&NS, coenzyme Q10, and fatigue

Coenzyme Q10 deficiency together with elevated levels of oxidative stress and mitochondrial dysfunction has been detected in plasma or white blood cells of patients with CFS [241, 242] and fibromyalgia [243–246]. Interestingly, the level of coenzyme Q deficiency is associated with the severity of fatigue, pain, and neurocognitive deficits experienced by patients with CFS [241].

A number of treatment studies with coenzyme Q10, typically at doses of 300 mg/day, have demonstrated significant improvements in markers of O&NS, mitochondrial biogenesis and ATP generation following supplementation, which correlated significantly and positively with reductions in pain and fatigue in people with a diagnosis of fibromyalgia [246, 247]. These results are very much in line with other studies examining the benefits of coenzyme Q10 on ATP generation and improved mitochondrial function [248]. There is also good evidence for objective improvements in muscle function and muscle fatigue at relatively high doses and or long durations of treatment [249, 250]. Confidence in the effectiveness and safety of coenzyme Q10 supplementation has been further increased by a recent landmark study by Alehagen et al. [251] where 200 mg of coenzyme Q10 daily given for 4 years produced an absolute reduction of cardiovascular mortality of 6 % compared to control with minimal side effects in a population or elderly patients. The favorable safety profile of far higher doses (>2 g daily) was established in studies examining the effects of coenzyme Q10 supplementation in Parkinson's disease [248].

IO&NS pathways, the master gene PGC-1α, and fatigue

The PGC-1 family of transcription factor orchestrates the regulation of energy metabolism. Their expression activates the transcription of regulatory genes involved in driving an increased capability for energy generation [252]. Animal experiments involving ablation of the PGC-1a gene demonstrated a diminished expression of genes governing fatty acid oxidation, the KREBS cycle, and oxidative phosphorylation [253]. There is growing evidence implicating impaired PGC-1 expression in the development of mitochondrial dysfunction and neurodegenerative processes [254–256]. Dysregulated expression of this transcription factor is involved in the etiopathogenesis of Parkinson's disease [255]. Reduced expression of PGC-1a found in the brains of multiple sclerosis patients is associated with decreased mitochondrial membrane potential, reduced production of proteins associated with oxidative phosphorylation, and cellular antioxidant defenses. It is particularly noteworthy that decreases in all these parameters correlate significantly and positively with loss of cortical neurons [256].

PGC-1a also plays a crucial role in regulating muscle performance and long-term adaption to exercise and hence chronic downregulation of this transcription factor which can occur in an environment of chronic oxidative stress, as discussed below, can have serious consequences for exercise performance in an affected person. Elevated levels of this transcription factor, which takes place during exercise, drives a switch from fast type II striated muscle fibers, which rely on ATP produced by glycolysis as their energy source, to slow type I muscle fibers utilizing energy produced by mitochondrial respiration [257, 258]. PG1-a activity regulates glucose and fatty acid refueling of exercising muscle by promoting fatty acid oxidation [259, 260] and lactate homeostasis and hence its expression may be responsible for delaying exercise-induced accumulation of lactate in striated muscle [257]. The sum of these positive actions is responsible for conferring resistance to exercise-induced muscle fatigue [233]. The loss or under-expression of the PGC-1a gene makes individuals and animals prone to develop muscle fatigue at a much less intense or prolonged level of exercise than control subjects [260, 261]. For example, mitochondrial dysfunctions and lowered levels of PGC-1α, a trigger of mitochondrial biogenesis, may cause muscle weakness, fatigue and exercise intolerance [262]. Other data show that Korean mistletoe extract improves endurance capacity in mice by activating mitochondrial activity probably through enhancing effects on PGC-1α [263]. PGC-1α additionally promotes resistance to muscle fatigability by driving fiber type switching possibly via effects on intracellular calcium levels [259]. Muscle PGC-1α knockout animals show lowered endurance capacity and more fiber damage and increased inflammation following exercise [264].

Given that elevated levels of TNFα leads to the downregulation of PGC-1α [265, 266], it is tempting to speculate that insufficient levels of this transcription factor contribute to the severe muscle fatigability seen in many patients with a diagnosis of CFS. There is as yet no evidence of this but this possibility would seem to be worthy of further investigation. Clearly, however, decreased levels of PGC-1a expression lead to impairments in oxidative phosphorylation which lead to dramatically elevated ROS production by mitochondria within myocytes [21, 78]. To make matters worse, diminished PGC-1α expression also impairs the activation of the antioxidant defense systems needed to resist the damaging effects of increasing radical species in a toxic cellular environment [267, 268].

IO&NS pathways, brain dysfunctions, and fatigue

Several areas within the brain and in particular the anterior and/or posterior cingulate gyrus and the insular cortex have been implicated in the development of fatigue [166, 269]. PET

scan studies using healthy volunteers examining regional blood flow during a fatiguing task have revealed that the medial orbitofrontal cortex exhibits a positive correlation in activity with fatigue (Brodmann's area 10/11), providing good evidence that the medial orbitofrontal cortex is a region of the brain whose activity is closely associated with generating mental fatigue [270]. In neurological disorders, pathological changes within the structures of the frontal cortex and deep gray matter are neural correlates of the development of pathological fatigue [271]. Fatigue in different clinical populations has additionally been linked with changes in brain structures, such as the ascending reticular formation [272], the monoaminergic nuclei [273], and the frontostriatal network [271].

A study using positron emission tomography to examine the effects of IFNα on fatigue revealed the existence of an elevated metabolism of glucose in the basal ganglia [274]. The presence of elevated glucose metabolism in the putamen and nucleus accumbens correlates significantly with patient reports of fatigue [275]. This distribution of increased basal ganglia glucose metabolism is strikingly similar to that found in Parkinson's disease [276]. Functional magnetic resonance imaging has also revealed denuded levels of neural activation in the basal ganglia in patients subjected to exogenously administrated IFNα [92]. Inoculation of healthy volunteers with LPS or typhoid vaccine (which are both inducers of pro-inflammatory cytokines) has been demonstrated to produce similar responses in the basal ganglia, indicating that administration of IFNα and other inflammatory inputs yield similar effects [277, 278].

Dysfunction in prefrontal cortex activity is thought to play a significant role in generating fatigue in patients with neuroimmune disorders, such as multiple sclerosis [279, 280] and CFS [281, 282]. Numerous studies have confirmed significant associations between abnormalities in the ventromedial prefrontal cortex and fatigue levels in multiple sclerosis [283, 284] and yet further support for this position stems from the fact that trauma based disruption of the ventromedial prefrontal cortex results in the production of severe chronic fatigue [285]. Pardini et al. [286] using fMRI investigated the brain areas associated with the generation of fatigue in patients with multiple sclerosis with minimal levels of disability who nevertheless suffered from severe fatigue. The authors actually detected a positive correlation between severe chronic fatigue and accuracy levels in timed tasks which they described as a "fatigue-motor performance paradox" mediated by oribitofrontal cortex and cerebellar activity [286]. Cortical atrophy involving the posterior parietal lobe (a region playing a major role in information integration and motor planning) also displays robust associations with the sensation of fatigue indicating that impairments in higher order parameters of motor control also play a large part in determining levels of fatigue in multiple sclerosis [287].

Many people with a diagnosis of CFS display significant lateral prefrontal cortex gray matter volume reductions [281, 282]. Cook and fellow workers examined the brain regions associated with reported fatigue during a task designed to generate cognitive fatigue in patients with CFS using functional MRI technology. The authors detected positive relationships between fatigue sensation and responsiveness in the cerebella, cingulate, frontal, temporal, and cerebellar regions [288]. Another study involving patients with CFS demonstrated increased fMRI activation in the posterior cingulate gyrus and in the occipitoparietal cortex, together with impaired activation in the dorsolateral dorsomedial and prefrontal cortices during fatigue provocation [289]. Significant reductions in gray matter volume located primarily in the prefrontal cortex have also been reported in many people afforded a diagnosis of CFS [281, 282] and decreased glucose metabolism in the prefrontal and orbitofrontal cortex is also seen in people with this illness. Hypoperfusion of the brain and brainstem also appears to be widespread in such patients [290, 291]. It is worthy of note that decreased cerebral blood flow in deep gray matter associated with fatigue development in some people with a CFS diagnosis is associated with the severity of fatigue in multiple sclerosis [292, 293]. Similar widespread reductions in blood flow are seen in depression and appear to be state related [294].

The consequences of such disruption are not immediately apparent until it is realized that the prefrontal territories are involved in effort evaluation and other cognitive tasks and hence dysfunction in these areas may well underpin the development of chronic fatigue [295, 296]. Rich connections exist between medial prefrontal structures and regions such as the hypothalamus, which play pivotal roles in regulating visceromotor and neuroendocrine responses [297] and the orbital prefrontal cortex which receives and integrates sensory information from virtually every system [298]. All in all, the weight of evidence demonstrates that the ventromedial prefrontal cortex plays an indispensable role in the selection and evaluation of motor and cognitive outputs and is the region of the brain responsible for a "cost benefit analysis" of and given activity [295, 296]. It is thus hardly surprising that disruption of this area produces sensations of severe mental fatigue [285].

IO&NS pathways, muscle dysfunctions, and fatigue

Muscle fatigue and impaired feedback from muscle afferents

Muscle fatigue is a common occurrence in a range of autoimmune diseases including systemic lupus erythematosus [299, 300], Sjögren's disease [301, 302], and rheumatoid arthritis [303, 304], and is a diagnostic criterion for CFS. Severe muscle fatigue and weakness is one of the most disabling features in the overall motor impairment in Parkinson's disease [305, 306]. de Haan and fellow workers reported that the disabling levels of muscle fatigue suffered by people with multiple sclerosis was not due to reduced muscle usage but rather to lower oxidative capacity in the muscle groups studied [307]. Steens et al.

reported a central contribution to the muscle fatigue experienced by patients where there was an inadequate increase in cortical activation to compensate for changes in voluntary activation [308]. This built on an earlier study by the same team which noted impaired voluntary activation in multiple sclerosis patients and, for the first time, demonstrated a positive relationship between objective measures of muscle fatigue and perceived levels of general fatigue in patients suffering from this illness [309]. Many patients afforded a diagnosis of fibromyalgia also suffer from pathological levels of muscle fatigue linked to mitochondrial dysfunction within the affected muscle groups. However, other patients diagnosed with fibromyalgia seem to have muscle fatigue resulting from central motor control failure [310, 311] and yet others display muscle membrane abnormalities as evidenced by surface EMG readings [312]. Muscle fatigue can be defined as a reduction in maximal voluntary muscle force induced by exercise. It may result from a combination of factors which include muscle level peripheral changes and central nervous system failure to adequately drive motor neurons. All in all, the multiple lines of evidence demonstrate that muscle fatigue is not simply resident in striated muscle [313].

Maximal muscle voluntary activation is in general significantly lower than maximal muscle force and furthermore this level of voluntary activation decreases rapidly over time. Voluntary activation of elbow flexor muscles for example may be optimal when performing maximal voluntary muscle force of relatively short duration but central fatigue quickly develops when the muscle contractions are repetitive or sustained [314, 315] due at least in part to decreased rate of firing of motor neuron units [316]. The origin of fatigue during maximal voluntary muscle force is primarily located in muscles but some originate from progressive decrease in voluntary activation of muscle, which is termed central fatigue, and also as a result of impaired output signals from the motor cortex [317].

Central fatigue appears to originate in regions of the brain located upstream the motor cortex [317]. Central fatigue is defined as the inability of the CNS to drive motor neurons efficiently via the exertion of powerful inhibitory effects on central motor drive during the performance of intermittent or prolonged aerobic exercise [318]. Changes in cortical and spinal neuron activity take place during the development of muscle fatigue, but their effects are separate from supraspinal fatigue, which is generated as a result of firing of fatigue sensitive muscle afferent fibers which act to decrease the voluntary descending drive [317]. The weight of evidence indicates the existence of two different types of muscle receptors with different responses following mechanical stimulation [319]. The bulk of these sensory afferents are group III. It is however worth emphasizing that a minimum of 40 % of group IV afferents are likely non-nociceptive [319]. There is now evidence that feedback from opioid-mediated, otherwise described above as group III and IV, muscle afferents conspire to inhibit central motor drive, thereby inducing central fatigue and limiting the development of peripheral muscle fatigue during exercise [318]. However, feedback from group III/IV muscle afferents exerts a number of different effects in addition to limiting central motor drive, importantly such feedback during aerobic exercise improves ventilatory and cardiovascular responses [320] and hence positively affects VO2 measurements. All in all, copious amounts of data exists demonstrating that opioid-mediated muscle afferents play a key role as part of a homeostatic mechanism designed to inhibit central motor drive thereby limiting muscle fatigue and perhaps permanent muscle damage [321]. Mechanistically, sensory information from muscle afferents activate an inhibitory system which inhibits primary motor cortex output in a phenomenon which is often described as supraspinal fatigue. In response to such inhibition, motivational systems activate in an attempt to compensate for this level of inhibition and ultimately the motor output is a resultant of the balance of activity between these inhibitory and facilitatory systems [322]. It is also worth noting, if just for the sake of completeness, opioid receptor-sensitive muscle afferents in the spinal chord also play a facilitative role in the muscle fatigue-induced increase in intracortical inhibition seen in exercising healthy humans [323].

Unsurprisingly, voluntary muscle contraction has been the focus of the majority of studies into muscle fatigue, but many lines of evidence now indicate that impaired function ultimately provoking voluntary muscle contraction failure likely occurs at all levels of the neuromuscular system. There is much debate over which mechanisms if any should be given primacy. Some authors argue most common failure stems from reduced motor command signal emanating from the motor cortex [324]. Noakes and fellow workers [325] have proposed that failures in voluntary muscle contraction emanate from the activity of a central comparator region in the prefrontal cortex capable of integrating homeostatic inputs from numerous physiological systems and then acting to terminate motor commands, via the activation of compensatory homeostatic systems, following sensory input from muscle afferents indicating the existence of sub-optimal energy resources. In this model, sensory fatigue is regarded as the conscious awareness of these homeostatic mechanisms at work [325].

IO&NS pathways, the sodium and potassium ion pump, and fatigue

Another source of muscle fatigue is the deleterious effects of prolonged ROS elevation on the sodium-potassium pump in muscle fibers whose optimum function is essential in prolonging muscle activity by minimizing fatigue. Interestingly, dysfunctions in the sodium potassium pump have been demonstrated in patients diagnosed with CFS [326], as well as depression and bipolar disorder [327, 328]. The sodium potassium ion pump plays a major role in the function of skeletal muscle by regulating concentration gradients of sodium and potassium across cellular membranes. The contractions

of skeletal muscle induce a profound loss of potassium ions (K+) and gain of sodium ions (Na+) within muscle cells [329], in spite of a marked compensatory increase in the Na+/K+-ATPase sodium potassium pump [330]. Therefore, this pump is a crucial player in minimizing muscle Na+ and K+ disturbances, and consequently in the preservation of membrane excitability and production of muscle force [329, 330].

Numerous studies indicate significant perturbations in muscle K+ homeostasis in exercising humans, which correlate positively with the development of fatigue [331, 332]. Several authors have proposed that elevated levels of ROS, normally produced during contractions of skeletal muscle during exercise could act to depress the optimal activity of the sodium potassium pump thereby providing an important connection between elevated ROS and disturbed Na+ and K+ homeostasis [333, 334]. This pump has an optimal redox range [335, 336] and hence the well-established role of elevated ROS in generating muscle fatigue [124, 334] stems, in a large part, from the inactivation of the sodium potassium ion pump [334].

The sodium potassium pump plays a crucial role in maximizing muscle performance and delaying and minimizing muscle fatigue during exercise [334, 337]. McKenna et al. found that the exercise-induced attenuation of sodium potassium pump activity was significantly improved by *N*-acetyl cysteine as evidenced by the lowering of the exercise-induced elevation of plasma [K+] thereby indication a strong association between ROS and inactivation of sodium further implicating ROS, and reduced sodium potassium pump and K+ activity in muscle fatigue [334]. This is clearly a likely mechanism by which prolonged oxidative stress could cause muscle pathology in people with CFS [326].

Increased muscle glutathione, cysteine, and increased muscle *N*-acetyl cysteine would all act to remove ROS from muscle cells and could thus protect the sodium potassium pump from the damaging effects of increased oxygen radicals. This proposition is consistent with other lines of evidence demonstrating that endogenous ROS scavengers such as catalase superoxide dismutase [338] and antioxidant agents such as dithiotreitol cysteine [339], α-tocopherol, carnosine [336], and histidine [340] display protective effects against ROS-induced attenuation of sodium potassium pump activity. The improvement in sodium potassium ion pump activity with increased muscle glutathione and cysteine availability was also demonstrated with *N*-acetyl cysteine infusions [124]. *N*-acetylcysteine administered orally, or via infusion, acts as an antioxidant, reduces muscle fatigability and enhances ergonomic performance by attenuating the decrease in Na+/K+-pump activity caused by the elevated ROS levels accompanying aerobic exercise [124, 334, 341]. The positive effects are dose- and duration-related and objective improvements in mitochondrial membrane potential, VO2, antioxidant capacity, markers of ROS, and RNS tissue damage and immune profiles have all been reported [124, 334, 341–343]. The most striking benefits in humans with a disease associated with chronically elevated O&NS, such as CFS, appear to occur following prolonged administration at between 2.8 and 4.2 g/day [342]. However, as discussed previously, numerous studies have demonstrated increased levels of ROS and RNS during exercise [113, 114] and at physiologically normal concentrations these radical species are indispensable signaling molecules modulating several essential physiological processes in muscle cells in response to increased levels of exercise [344, 345].

IO&NS pathways and muscle metabolite built up

The role of metabolite buildup in signaling between the muscles and brain has been the subject of intense interest. Ion-sensing channels in muscle (acid-sensing ion channels) with the capability of detecting pH and ATP changes and activating sensory nerves once a pH threshold is exceeded facilitates this direct muscle brain signaling [346, 347]. These "acid-sensing" ion channels are predominant in sensory nerve fibers innervating skeletal muscle [166] and have the capacity to detect pH changes in contracting muscle. The sensory nerve fibers containing acid-sensing ion channels are located on the exterior surfaces of venules and arterioles located in the fascia surrounding the muscles [348]. Although incapable of initiating the activity of sensory neurons on its own, ATP, at the trace concentrations located in muscle interstitium in contracting muscles, greatly increases the sensitivity of acid-sensing ion channels to pH and lactate thereby maintaining the gated current needed to activate sensory muscle afferents [346, 347]. The weight of evidence now indicates that the receptors mediating responses to these metabolites are a number of purigenic receptors a P2 acid-sensing ion channel receptor. Several combinations of metabolites produced in fatiguing muscles have the capacity of activating dorsal root ganglion neurons [346, 347] which are exquisitely sensitive to combinations of ATP, protons and lactate at the normal physiological range of concentrations [349].

There is some interesting research implicating abnormalities in the transcription of the above receptors in fatigue generation in a cohort of people diagnosed with CFS [350]. This is particularly noteworthy in the light of the fact that the cardinal hallmark of the illness in many people is dramatically increased muscle fatigue and pain following even trivial increases in exercise [351] and minor exercise dramatically increases their other symptoms [166]. Light et al. compared longitudinal adrenergic α2, β1, and β2 receptors, IL-6, IL-10, TNFα, TLR4, and CD14 expression in the muscles of patients with a diagnosis of CFS under the CDC 1994 criteria compared to healthy controls [166, 350]. While the latter displayed no statistically significant increase in mRNA for any of the receptor genes examined, CFS patients displayed significant elevations in the expression in virtually all of these genes (save for IL-10 and IL-6) as soon as 30 min after the

commencement of moderate exercise and were of far greater magnitude than seen in controls at maximal exercise. The authors additionally noted strong positive correlations between elevations in mRNA of adrenergic β1, β2, adrenergic TLR4, IL-10, α2A, COMT, and CD14 in CFS patients and numerous measurements of mental fatigue in the aftermath of the experiments which persisted for 48 h. The abnormalities discussed above could be a major contribution to the profound pathological levels of fatigue suffered by these patients.

IO&NS pathways, heat shock proteins, and fatigue

Lower baseline levels of heat HSPs, including HSP70 and HSP27, are observed in some patients with CFS [105]. Levels of HSP27 in lymphocytes and monocytes are additionally significantly and positively correlated with fatigue resistance [352]. A number of vital cytoprotective effects have been assigned to HSPs, especially the HSP70 group. They essentially cover chaperone activities being involved in the management of protein disposal folding, correction of misfolding, prevention of protein accumulation, and escorting proteins across external and internal cellular membranes [353]. HSPs provide cellular protection in the face of various stressors such as increased oxidative stress, and activation of proteases and release of proteolytic enzymes [354]. Many stress signals are capable of activating HSP transcription and promoting post translational modification including energy depletion and generation of ROS [355]. HSPs serve to modulate signals initiated by immune-inflammatory responses, in particular those leading to the production of cytokines [356]. Increases in the levels of intracellular HSP levels improve cell resistance to pro-inflammatory cytokines such as IL-1 and TNFα [357] and decreases their production [358]. However, when HSPs located on or within cells escape into the extracellular environment following necrotic cell death or viral infection, these proteins activate and enhance the immune response. Hsp70 also facilitates antigen presentation and provoke cytokine production in antigen presenting cells (APGs) such as dendritic cells and macrophages [359, 360].

Several authors have demonstrated acute exercise results in the production of elevated levels of heat shock proteins in contracting skeletal muscle [361]. The situation in many patients diagnosed with CFS is however entirely atypical. Such patients demonstrate abnormal HSP responses during exercise and for a prolonged period thereafter [362]. Many patients with CFS additionally display low baseline levels of certain HSPs and an impoverished and delayed increase during exercise [104, 105]. This becomes even more intriguing in the light of evidence that HSP70 and HSP27 fail to rise during exercise in patients who report an infective origin of their symptoms but not in those who do not [105]. Intriguingly, many viruses implicated in the development of symptoms in at least some patients with CFS such as Epstein Barr and other herpes viruses suppress production of host HSPs [363]. Elevated levels of HSPs during exercise protect muscle lipids, proteins, and DNA against the corrosive effects of elevated oxygen and nitrogen species [364, 104] and hence the pathological consequences stemming from the failure of this cytoprotective system cannot be overstated.

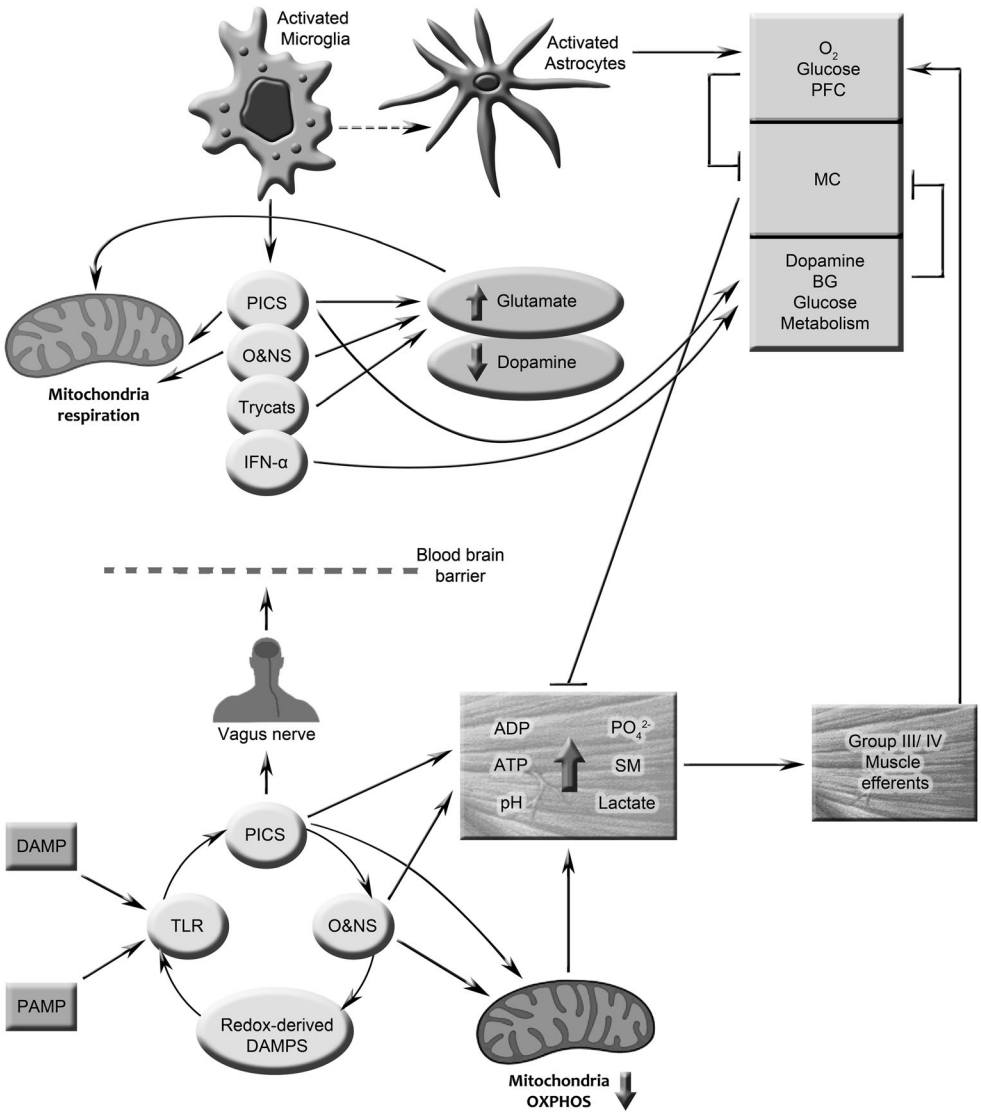
IO&Ns pathways, mitochondria, and muscle fatigue

O&NS signals adversely affect mitochondrial morphology and function in skeletal muscle [344, 345]. ROS are produced at a multiplicity of sites within muscle fibers including the metabolism of arachadinonic acid, phospholipase A2, and the activity of the electron transport chain within mitochondria [365, 366, 21]. Mitochondrial dysfunction in particular is known to be a source of elevated cellular ROS levels [21]. Oxidative stress corrupts muscle components via lipid peroxidation [367], oxidation of mitochondrial and nuclear DNA [368], protein carbonylation [369], tyrosine nitration [369], and thiol group oxidation [367]. A number of elements crucial for the optimal performance of muscles contain thiol proteins and are hence highly vulnerable to oxidative stress induced dysfunction. They include the ryodine receptor calcium ion release channel [370], SR Ca2+ ATPase [371], troponin [372], tropomyosin [373], myosin [374], and actin [375]. All in all, it is clear that a number of thiol-regulated proteins mediate muscle fatigue induced by oxidative stress and resultant thiol oxidation but the proteins contained within the Na+/K+ ATPase pump as discussed above appear to be the most important [115, 376].

Fig. 2 Prolonged tissue inflammation as a result of a protracted immune activation or other inflammatory insult leads to chronically elevated levels of pro-inflammatory cytokines (PICs) and oxidative and nitrosative stress (O&NS) leading to damage of proteins, lipids, and DNA. Some of these damaged molecules may consecutively function as redox-derived damage-associated molecular patterns (DAMPs) capable of activating toll-like receptors (TLR) which once activated lead to the production of more PICs, O&N species and thus redox-derived DAMPs. In this manner, once activated by PAMPs and DAMPS, an environment of chronic immune activation and inflammation in the periphery may become self-sustaining and self-amplifying in a TLR radical cycle leading to damage to mitochondria impaired OXPHOS and direct inhibitory effects on muscle function. Signals of peripheral inflammation can reach the brain leading to the activation of microglia and astrocytes. This signaling is mediated directly by PICs in the circulation which can enter the CNS via a number of routes or via the activation of the vagus nerve. Once activated, astrocytes and microglia produce neuromodulatory and neurotoxic substances including tryptophan catabolites (TRYCATs), PICs, IFNα, and O&NS. PICs and TRYCATs conspire to raise glutamate and decrease dopamine levels while activated astrocytes and IFNα can adversely affect glucose metabolism and perfusion levels throughout the brain. These abnormalities could explain the development of severe intractable fatigue in neuro-immune and autoimmune diseases. In normal circumstances, muscle fatigue during exercise is facilitated by group III/IV afferents activated by the presence of certain metabolites which relay information to the prefrontal cortex which in turn inhibits muscle function. The metabolites in muscles resulting from chronic inflammation could lead to chronic activation of these efferents and chronic inhibition of muscle function

Discussion

We aimed to review the evidence indicating that a range of systemically elevated pro-inflammatory cytokines are intimately involved in the genesis and maintenance of the pathological levels of fatigue endured by people suffering from cancer and a range of neuro-psychiatric, neuro-inflammatory, and autoimmune diseases. Figure 2 shows the different pathways that may cause fatigue. Overall, the evidence implicating a causal role for pro-inflammatory cytokines, at least in part, in the onset of fatigue is persuasive. The weight of evidence indicates that elevated levels of pro-inflammatory are also intimately involved in the genesis and maintenance of neuro-inflammation and chronic disruption of the BBB. Neuro-inflammation, invariably accompanied by disruption of the BBB, is causatively implicated in the development of mental fatigue.



ADP: Adenosine diphosphate
ATP: Adenosine triphosphate
BG: Basal ganglia
DAMP: Damage associated molecular pattern
IFN-α: Interferon alpha
MC: Motor cortex
O&NS: Oxidative and nitrosative stress
OXPHOS: Oxidative phosphorylation
PAMP: Pathogen associated molecular pattern
PFC: Prefrontal cortex
PICS: Pro-inflammatory cytokines
PO_4^{2-}: Phosphate anion
SM: Striated muscle
TLR: Toll-like receptors
Trycats: Tryptophan catabolites

The effects of elevated O&NS in generating muscle fatigue and chronic muscle pathology are well documented and the corruptive effects of ROS and RNS on proteins with an essential role in muscle function are equally well reported. The corrosive effects of O&NS extend to the inactivation of the sodium potassium pump which impacts muscle performance and fatigue. Activation of the TLR2/4 Radical cycle by DAMPs including heat shock proteins may drive chronic inflammation and O&NS processes thereby further activating the pathways to chronic fatigue. Limited adaptability of mitochondria to increase energy output and mitochondrial dysfunctions, potentially secondary to elevated O&NS is another plausible explanation for the existence of peripheral and central fatigue.

Excessive levels of cytokines are also known to disrupt dopaminergic neurotransmission particularly in the basal ganglia which is a region of the brain seemingly involved in the genesis of fatigue in many neurological illnesses. The capacity of elevated cytokines to impede reuptake of glutamate by astrocytes is another commonly reported phenomenon. The proposal that elevated levels of extracellular glutamate underpins, at least in part, the development of cognitive or mental fatigue, is intriguing. The evidence that neuro-inflammation and BBB disruption make independent contributions to increased levels of extracellular glutamate strengthens both the argument that abnormal glutamate levels are involved in the genesis of mental fatigue and that elevated levels of pro-inflammatory cytokines drive abnormal glutamate levels. Another indirect route by which elevated levels of pro-inflammatory cytokines in the periphery and or the CNS might cause cognitive fatigue is via the production of tryptophan catabolites once again adversely affecting glutaminergic and dopaminergic neurotransmission. IFNα disrupts glucose homeostasis in the basal ganglia and suppresses neural activity in the same region, both potential causes of cognitive fatigue.

While the abovementioned neuro-immune abnormalities may be important generators of chronic fatigue, other central and peripheral mechanisms could account for the presence of central and peripheral chronic fatigue. Functional and structural abnormalities in several brain areas are implicated in the genesis of chronic fatigue. The most common areas cited being the frontal and prefrontal cortex and the basal ganglia. It is however entirely possible that activation of microglia and the adverse effects of pro-inflammatory cytokines and IFNα could be the source of dysfunction within the basal ganglia so often implicated in the genesis of fatigue. Other studies place specific emphasis on structural and functional abnormalities within gray matter such as low oxygen perfusion levels and impaired glucose metabolism, both of which could result from reactive astrogliosis and hence once again these observations could ultimately flow from the results of activated immune and inflammatory pathways in the periphery.

Peripheral fatigue involves muscle weakness which can originate within muscles (e.g., muscle opioid receptors, muscle membranes, toxic levels of chemical entities within muscles) and central components originating from multiple levels of the neural axis (e.g., higher brain centers, motor cortex, and spinal cord). These elements are all involved in the homeostatic control of muscle function aimed at preserving muscle function and preventing muscle damage during exercise. Abnormalities in the transcription of receptors on muscle membranes which communicate information about levels of toxic metabolites to the brain, via the activation of dorsal root ganglion neurons, is another potential mechanism whereby muscle fatigue can occur at unusually low levels of effort. There may also be an intriguing connection between a state of chronic inflammation in the muscles and the development of sensory fatigue. It is noteworthy that the toxic milieu of metabolites which activates group III/IV efferents, resulting in inhibition of muscle performance, is chronically present in muscle in a state of chronic inflammation with elevated O&NS and TNFα. Much of this milieu is created as a result of impaired oxidative phosphorylation and cellular stress. The point however is that this is very much part of the danger signal which activates an inhibitory response from the prefrontal cortex and would at least theoretically result in chronic inhibition of muscle function and a severely compromised ability to exercise. Under the model proposed by some authors, the homeostatic mechanisms normally responsible for protecting muscles from exercise-based damage would also be chronically activated and chronic sensory fatigue would result from a conscious interpretation of these homeostatic mechanisms in action.

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