Leaky gut in chronic fatigue syndrome: A review

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Abstract

There is now evidence that the pathophysiology of chronic fatigue syndrome (CFS) is related to inflammation and oxidative & nitrosative stress (IO&NS) with a) signs of immune activation and a suppression of ex vivo cellular immune responses; and b) damage to membrane lipids, functional proteins and DNA by O&NS. The above disorders are mediated by intracellular inflammation as indicated by an increased production of nuclear factor kappa Beta (NFκB), cyclo-oxygenase-2 (COX-2) and inducible NO synthase (iNOS). The above inflammatory reactions may be activated by a number of etiological factors, e.g. psychological stress, strenuous exercise, viral and bacterial infections. The purpose of this paper is to review the evidence that an increased translocation of gram negative bacteria is another inflammatory pathway that is involved in CFS. The serum concentrations of IgM and IgA to lipopolysaccharide (LPS) of gram-negative enterobacteria, i.e. Hafnia Alvei; Pseudomonas Aeruginosa, Morganella Morganii, Pseudomonas Putida, Citrobacter Koseri, and Klebsielle Pneumoniae are significantly increased in patients with CFS. This suggests that in CFS there is an increased LPS translocation through a weakened tight junction barrier with subsequent gut-derived inflammation. This condition indicates an increased gut permeability or leaky gut. Treatment for 10-14 months with specific anti-inflammatory and -oxidative substances (NAIOSs), such as glutamine, N-acetyl cysteine and zinc, with or without immunoglobins intravenously (IVIg), significantly attenuates the initially increased IgA and IgM responses to LPS, showing that the gut-derived inflammation is attenuated and thus that the weakened tight junction barrier is partly restored. The attenuation of gut-derived inflammation predicts the clinical improvement 10-14 months after intake of NAIOSs. The above findings show that an increased translocation of gram negative bacteria with subsequent inflammation is a new pathway that contributes to the systemic IO&NS responses in CFS.

Introduction

Chronic Fatigue Syndrome (CFS) is a medical illness that is characterized by specific symptoms, such as fatigue, pain, infectious and neuropsychiatric symptoms (Fukuda et al 1994). Typical symptoms are substantial impairment in short–term memory or concentration; sore throat; tender cervical and axillary lymph nodes; muscle pain; multi–joint pain without selling or redness; headache of new type; unrefreshing sleep; post exertion malaise lasting more than 24 hours; and symptoms of irritable bowel syndrome (IBS). The symptoms must have persisted for at least six months (Fukuda et al 1994).

There is now evidence that CFS is an immune disorder characterized by an induction of inflammatory and oxidative and nitrosative stress (IO&NS) pathways.
1. Systemic inflammatory responses in CFS

A systemic inflammatory response is indicated by a number of findings. An increased production of pro-inflammatory cytokines, such as interleukin-1 (IL-1), IL-6 and tumor necrosis factor-α (TNFα). There is also an increased expression of T cell activation markers, such as CD26 and CD38, suggesting immune activation. Indicators of a peripheral inflammatory response are increased plasma concentrations of alpha-2 globulins, as obtained by electrophoresis, and decreased serum zinc levels (Aoki et al 1993; Barker et al 1994; Klimas et al 1990; Visser et al 1998; Patarca et al 1994; Linde et al 1992; Lloyd et al 1992; Gerrity et al 2004; Maes et al 2006a). Also, the suppression of ex vivo cellular immune responses, such as decreased mitogen-induced lymphocyte responses and mitogen-induced expression of CD69 indicates the presence of an immune response (Mihaylova et al 2007). It is also known that viral infections, e.g. with Epstein–Barr Virus may induce CFS. EBV viremia in CFS is accompanied by systemic inflammation, as indicated by an increased degradation of tryptophan (Bellmann-Weiler et al 2008). The catabolism of tryptophan is typically enhanced by pro-inflammatory cytokines, such as interferon-γ (IFNγ) and IFNa. Those cytokines can induce indoleamine 2,3-dioxygenase (IDO), the enzyme that converts tryptophan into tryptophan catabolites along the IDO pathway (TRYCATs) (Maes et al 2007a). In the former study, the authors (Bellmann-Weiler et al 2008) found that the serum concentrations of neopterin are positively correlated to signs of tryptophan degradation, suggesting that CFS patients due to EBV infection suffer from IFNγ-induced activation of cell-mediated immunity. These findings suggest that induction of IDO with an activation of cellular immunity and decreased plasma tryptophan are related to chronic fatigue following viral infections.

Also experimental induced inflammation is accompanied by fatigue. Thus, IFNa-based immunotherapy in HCV patients (hepatitis-C virus) has been shown to induce fatigue and “psychosomatic symptoms”, including pain (Wichers et al 2005; Martin et al 2007; Bull et al 2008). These symptoms appear after starting the treatment. This indicates that fatigue, pain and psychosomatic symptoms are early signs of cytokine-induced inflammation. It is also known that IFNa-based immunotherapy can induce depression and even full blown major depression in a considerable number of HVC patients. However, the depressive symptoms occur some weeks after starting the treatment (Wichers et al 2005). Thus, it appears that fatigue/pain and depression are two different signs of inflammation: the former appearing some days after starting treatment, the latter appearing some weeks later. Also, the depressive reactions are predicted by the degree of fatigue one week after starting cytokine treatment (Wichers et al 2005). There is another argument showing that both symp-
blood cells (RBC) and to hemoglobin (Richards et al 2007). The latter may indicate that the RBC membrane of patients with CFS are damaged and that the peroxycylic membrane bilayer has become more rigid (Richards et al 2007).

3. Intracellular inflammation

Recently, we detected that there is an intracellular inflammation in CFS. A major finding is that the production of nuclear factor kappa beta (NFκB), and the inducible enzymes cyclo-oxygenase-2 (COX-2) and inducible NO synthase (iNOS) are significantly increased in CFS (Maes et al 2007c; 2007d). These findings are also corroborated by gene expression studies which observed an increased NFκB gene expression in CFS (Kerr et al 2008). NFκB is the major intracellular mechanism that regulates and induces the IO&NS pathways (Brasier 2006). Once induced, NFκB will be translocated from the cytoplasm to the nucleus of the cell. In the nucleus NFκB binds with DNA promoter sequences to induce transcriptional activation of IO&NS pathways, such as COX-2, iNOS, and pro-inflammatory cytokines, such as IL-1β, IL-6, and TNFα (Brasier 2006). COX-2 is another key enzyme that is induced during inflammation. COX-2 is involved in the synthesis of prostaglandins and prostacyclins (Feng et al 1995). Upon stimulation, iNOS will generate nitric oxide (NO) by macrophages and neutrophils (Lipton 1996; Brown 1999). As explained above NO plays an important role in generating damage caused by O&NS. We found that - in CFS - the production of NFκB was significantly related to the production rates of both iNOS and COX-2 which shows that the increased production of NFκB drives the higher production rates of iNOS and COX-2 (Maes et al 2007c).

Therefore, we have argued that the peripheral signs of systemic IO&NS, as discussed above, should be attributed to intracellular inflammation. Indeed, NFκB may induce the production of the IO&NS pathways, such as that of the pro-inflammatory cytokines, which in turn can induce signs of systemic inflammation, such as decreased zinc and changes in acute phase proteins (Maes et al 2007c; 2007d). Moreover, the induction of COX-2 and iNOS is responsible for further induction of more IO&NS pathways, with causes an increased production of prostaglandins, NO, superoxide, peroxynitrite and eventually to the damage to proteins and fatty acids with the formation of neoepitopes which in turn will induce greater and more responses in the IO&NS pathways (Maes et al 2007c; 2007d).

4. Systemic and central inflammation and the symptoms of CFS

Systemic inflammation is often accompanied by central neuroinflammation. For example, challenge with LPS induces an activation of brain microglia with a chronically elevated production of pro-inflammatory mediators, such as TNFα (Qin et al 2007). The latter may remain elevated during 10 months (Qin et al 2007). Peripheral or central administration of LPS thus may cause brain neuroinflammation and an increased production of pro-inflammatory cytokines, such as IL-1β, IL-6 and TNFα, which in turn may induce specific symptoms, labeled as the sickness behavior syndrome (Qin et al 2007). As explained (Maes et al 1993; 2009), there is a strong similarity between the symptoms of sickness behavior, on the one hand, and those of depression (anorexia, weight loss, psychomotor retardation, anhedonia) and CFS (fatigue, pain, sleep disorders, soporific effects, cognitive disorders), on the other. In both disorders, there are highly significant correlations between sings of inflammation and the key symptoms of depression or CFS, which indicates that the symptomatology of both disorders is related to IO&NS. Thus, in depression, there is a strong correlation between serum haptoglobin levels (an acute phase protein) and the “psychosomatic” depressive symptoms, e.g. anorexia, weight loss, middle insomnia, psychomotor retardation, and loss of interest (Maes et al 1993; 2009). In CFS, we detected significant correlations between signs of IO&NS activation and specific symptoms: a) the serum IgM levels directed against fatty acids, MDA and azelaic acid are significantly related to aches and pain, muscular tension and fatigue (Maes et al 2006b); the serum IgM levels directed against Pi are significantly related to fatigue and depression (Maes et al 2007b); the IgM antibodies directed against the nitro-derivates of the amino-acids are significantly related to aches and pain, muscular tension and fatigue (Maes et al 2006b); and increased NFκB is significantly correlated to aches and pain, muscular tension, fatigue, irritability, sadness, and the subjective feeling of infection (Maes et al 2007c).

Recently, we have discussed that LPS administration and activation of the systemic IO&NS pathways are accompanied by increased levels of pro-inflammatory cytokines in the brain with activation of microglia and, thus, with neuroinflammation (Qin et al 2007). Previously we have discussed that the symptoms of CFS may be induced by a) intracellular inflammation with increased COX-2 and iNOS levels, which may induce pain, muscle pain, inflammatory malaise, neurocognitive disorders (Maes et al 2007c; 2007d); b) increased production of pro-inflammatory cytokines, which may induce fatigue, depression, and inflammatory malaise (Maes et al 2009); and c) damage caused by O&NS, which may induce fatigue, muscle pain, and muscle tension (Maes et al 2006b; Maes 2009). Administration of LPS may provoke comparable symptoms in animal models (Borowski et al 1998; Lacosta et al 1999). The above findings suggest that IO&NS may have induced the symptoms of CFS.

Act Nerv Super Rediviva Vol. 51 No. 1-2 2009

23
5. TRIGGER FACTORS FOR INTRACELLULAR INFLAMMATION AND CFS AS WELL

We have explained previously that CFS may be induced by a number of trigger factors, such as viral infections, psychological stress and sustained strenuous exercise (Maes 2009). Increased serum antibodies to Epstein-Barr virus (Lerner et al. 2004), human cytomegalovirus (Beqaj et al. 2008), herpes VI virus (Patnaik 1995), and human parvovirus B19 (Seishima et al. 2008) are present in CFS. Enterovirus VP1, RNA and non-cytopathic viruses are significantly more detected in the stomach of patients with CFS (Chia & Chia 2008). Therefore, it has been suggested that CFS may be due to persistent viral infections (Dowsett et al. 1990). These findings are corroborated by recent findings that treatment with valacyclovir for six months shows a significant efficacy in treating CFS by increasing energy levels (Lerner et al. 2007). Also, psychological stress is known to induce the IO&NS pathways, such as the production of pro-inflammatory cytokines (Maes et al. 1998); lipid peroxidation and oxidative/nitrosative DNA damage (Aleksandrovskii et al. 1988; Pertsov et al. 1995; Sivonova et al. 2004; Irie et al. 2001); and LPS-induced NFκΒ activation in the frontal cortex and the hippocampus (Munhoz et al. 2006). Sustained strenuous exercise throughout childhood and early adult life can increase the risk to develop CFS and to generate IO&NS (Orhan et al. 2004; Klapcinska et al. 2005), including increased NFκΒ in muscles (Kramer & Goodyear 2007). Thus, the various factors which are known trigger factors of CFS also induce the IO&NS pathways including the production of NFκΒ. Recently, we detected a new pathway that may induce systemic inflammation and that is related to CFS, i.e. an increased translocation of LPS with consequent gut-induced inflammation.

6. INCREASED TRANSLLOCATION OF LPS FROM GRAM NEGATIVE ENTEROBACTERIA

We found that the prevalences and median values for the plasma IgA and IgM levels directed against LPS of various enterobacteria (Hafnia Alvei; Pseudomonas Aeruginosa, Morganella Morganii, Proteus Mirabilis, Pseudomonas Putida, Citrobacter Koseri, and Klebsielle Pneumoniae) are significantly greater in patients with CFS than in normal controls (Maes et al. 2007e). This suggests that there is a systemic inflammation directed against LPS, which is induced by the presence of increased intestinal permeability (leaky gut) with enlarged spaces between the cells of the gut wall and a loss of the protective barrier. Such a phenomenon is known to cause an increased bacterial translocation and an increased translocation of LPS (endotoxin), which both cause increased LPS circulating levels in the peripheral blood and consequently an increased production of NFκΒ, which in turn can induce the IO&NS pathways (Maes et al. 2007e). Phrased differently, the increased plasma IgA and IgM levels against the LPS of gram negative enterobacteria in CFS indicate the presence of an increased gut permeability and a mounted immune response directed against LPS of the enterobacteria.

Leaky gut is known to be a driver of systemic inflammation (Wischmeyer 2006). For example, in abdominal postoperative patients increased gut permeability is a cause of systemic inflammation, while an attenuation of leaky gut is accompanied by a reduced systemic inflammation (Quan et al. 2004). The pathway which causes gut-derived inflammation is bacterial translocation or translocation of LPS from gram negative bacteria, whereby bacteria or LPS are increasingly translocated from the gut into the blood (Wischmeyer 2006; Quan et al. 2004). Phrased differently, “increased intestinal permeability” allows normally poorly invasive enterobacteria or the LPS from those bacteria to exploit the enlarged spaces to cross the gut epithelium (Wischmeyer 2006). The increased translocation of LPS or bacteria causes infections or induces the IO&NS pathways in the peripheral blood and liver through a primary induction of NFκΒ, which eventually induces central neuroinflammation.

We also detected significant correlations between the increased IgA-mediated immune response directed against LPS and muscular tension, fatigue, concentration difficulties, failing memory, autonomic disturbances, the subjective experience of infection and symptoms of IBS (Wischmeyer 2006). Thus, the relationship between the increased plasma IgA levels directed against LPS and IBS reflects gut-induced inflammation and not “mental stress” or “something in the mind” as most psychiatrists would posit. In our clinical experience IBS may precede CFS, while in other patients IBS develops together with the fatigue and pain symptoms or develops later in the course of illness. This suggests that “gut-derived inflammation” caused by increased LPS translocation may be a primary cause of CFS or may be a secondary phenomenon which may further aggravate the existing IO&NS. In any case, these results show that gram negative enterobacteria may be one of the etiological factors which can trigger CFS (Wischmeyer 2006).

7. CAUSES OF AN INCREASED GUT PERMEABILITY

The intestinal barrier may be compromised by various etiological factors which are also known to induce CFS or chronic fatigue due to an organic disorder or condition. These are amongst others: psychological stress (Meddings & Swain 2000; Cameron & Perdue 2005); sustained strenuous exercise (Davis et al. 2005); surgery and trauma (Riddington et al. 1996; Pape et al. 1994), alcoholism (Bjarnason et al. 1984), the use of non-steroid anti-inflammatory drugs (NSAIDs) (Bjarnason et al. 1984), chemotherapeutic agents (Coltart et al. 1988), prolonged use of antibiotics (Berg 1992; Viljoen et al. 1994). These are amongst others: psychological stress (Meddings & Swain 2000; Cameron & Perdue 2005); sustained strenuous exercise (Davis et al. 2005); surgery and trauma (Riddington et al. 1996; Pape et al. 1994), alcoholism (Bjarnason et al. 1984), the use of non-steroid anti-inflammatory drugs (NSAIDs) (Bjarnason et al. 1984), chemotherapeutic agents (Coltart et al. 1988), prolonged use of antibiotics (Berg 1992; Viljoen et al. 1994).

But also activation of the systemic IO&NS pathways induces disruptions of gut permeability. a) Pro-inflammatory cytokines, such as IL-1β, IL-6, TNFα, and IFNγ are known to induce leaky gut by causing a loss of the gut tight junction barrier (Clark et al 2005; Chavez et al 1999; Yang et al 2003; Al-Sadi & Ma 2007). This phenomenon entails an enlarging of the spaces between the epithelial cells surrounding the gut wall, causing an increased permeability of the gut (Clark et al 2005; Chavez et al 1999; Yang et al 2003; Al-Sadi & Ma 2007). NFκB is essential in the loosening of the intestinal epithelial tight junction barrier. Thus, the IL-1β-induced leaky gut is mediated by NFκB activation (Al-Sadi & Ma 2007). Also, the TNFα-induced opening of the tight junction barrier is mediated by NFκB p50/p65 binding (Ye et al 2006; Ma et al 2005). Oxygen free radicals also cause a disruption of the tight junctions and thus of the intestinal barrier (Sun et al 2002). It is interesting to note that a depletion in certain natural anti-inflammatory and anti-oxidative substances (NAIOSs), e.g. glutamine, increases the risk to develop bacterial translocation (Wu et al 2004).

In conclusion, leaky gut may activate IO&NS pathways through increased bacterial and LPS translocation but the activation of the IO&NS pathways may also cause an opening of the tight junction barrier. Thus, leaky gut may be a primary causative factor in CFS or may be a secondary factor which further aggravates an existing activation of the IO&NS pathways, thus inducing a vicious circle between IO&NS activation and weakening of the tight junction barrier.

8. Treatment of leaky gut and CFS

There is now evidence that NAIOSs, such as glutamine, NAC, and zinc, have significant effects in treating leaky gut (Wu et al 2004; Olanders et al 2003; Sturniolo et al 2001; Chen et al 2003). Glutamine administration a) may repair the openings of the tight junction barrier and may decrease bacterial LPS translocation (Wu et al 2004); b) attenuates gut injuries and therefore may decrease gut-derived inflammation (Wischmeyer 2006); c) increases transmucosal resistance and decreases the mannitol flux through the epithelium and the prevalence of systemic infections (Foitzik et al 1997); d) reduces gut damage caused by NSAIDs and the consequent bacterial translocation in the rat (Ann et al 2004); e) reduces gut permeability, serum LPS concentrations and sibs of systemic IO&NS (Quan et al 2004); f) improves gut permeability and decreases plasma LPS concentrations in injured patients (Zhou et al 2003); and g) significantly inhibits TNFα-induced bacterial translocation in caco-2 cells (Clark et al 2003). The abovementioned results show that glutamine is not only essential for the preservation of the functional tight junction barrier to microorganisms, but also that glutamine administration reduces leaky gut, the loosening of the tight junction barrier; bacterial LPS translocation, and gut-derived inflammation (Clark et al 2003; Buchman 1999). Zinc administration improves damaged rat intestines and stimulates gut repair and results in improved barrier integrity (Tran et al 1999; 2003; Di Leo et al 2001). Also, NAC administration tightens leaky gut and ameliorates gut-derived inflammation (Sun et al 2002).

Therefore, we have examined the effects of the above NAIOSs which had been taking during 12-14 months on the initially increased IgA and IgM responses to translocated LPS in patients with CFS (Maes et al 2007f; Maes & Leunis 2008). We found that the intake of those NAIOSs attenuates the increased IgM and IgA responses directed to LPS. This shows that these NAIOSs reduce gut-derived inflammation. By inference it may be deduced that these NAIOSs restore the loosened tight junction barrier. We found that the attenuation of the IgM responses directed to LPS was more pronounced than those in the IgA responses. We have explained this phenomenon because serum IgA responses indicate the more chronic pathogenic conditions (Maes & Leunis 2008).

Moreover, we found that the normalization of the IgA and IgM responses directed to LPS may in part predict the clinical outcome in CFS. Other predictors for a good outcome are: a younger age at onset of the CFS, the younger age of the patient and a shorter duration of the CFS (< 5 years). Thus, the attenuation of the translocation of LPS and consequently of the gut-derived inflammation predicts a better clinical outcome. These results support the view that restoration of the weakened tight junction barrier with reduced translocation of LPS by treatment with NAIOSs is accompanied by an improvement in some patients or with a total clinical remission in others. Thus, although improvement of gut-derived inflammation by NAIOSs is accompanied by a clinical improvement it is certainly not always accompanied by clinical remission. The above and the fact that the longer duration of illness is another risk factor for a worse clinical response indicates that other pathophysiological factors are involved. These may constitute: damage by O&NS to membrane fatty acids, functional proteins and DNA and autoimmune responses, which frequently occur in CFS.

In our published case report (Maes et al 2007f), the patient was treated with NAIOSs together with immunoglobulins intravenously (IVIg). IVIg is used since it is effective in reducing IO&NS reactions: this treatment reduces NFκB production; pro-inflammatory cytokine production; T-cell activation; and autoimmune reactions (since it contains antiidiotypic antibodies against human autoantibodies) (Garcia et al 2007; Skansen-Saphir et al 1998; Menezes et al 1997; Wu et al 2006; Makata et al 2006; Rossi & Kazatchkine 1989). Interestingly, IVIg also decreases bacterial translocation (Herek et al 2000). Thus, CFS patients with very severe leaky
gut together with severe IO&NS activation and autoimmune reactions can best be treated with the abovementioned NAIOSs together with IVlg.

In conclusion, gut-derived inflammation due to increased LPS translocation is a novel pathway in CFS. Leaky gut can be a primary cause of CFS or may develop during the course of CFS because the activated IO&NS pathways with increased cytokine and NFκΒ production induce a loosening of the tight junction barrier. The latter can be treated by specific NAIOSs with or without IVlg which in turn may have a clinical efficacy in patients with CFS who suffer from leaky gut. However, this treatment is rather expensive and takes 10–14 months. Therefore, leaky gut is a new drug target to develop novel drugs useful in treating leaky gut and CFS.

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Leaky gut in chronic fatigue syndrome


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