Fatigue in liver disease: Pathophysiology and clinical management

Mark G Swain MD MSc FRCP

Fatigue is the most commonly encountered symptom in patients with liver disease, and it has a significant impact on their quality of life. However, although some progress has been made with regard to the understanding of the processes which may generate fatigue in general, the underlying cause(s) of liver disease-associated fatigue remain incompletely understood. The present review describes recent advances which have been made in our ability to measure fatigue in patients with liver disease in the clinical setting, as well as in our understanding of potential pathways which are likely important in the pathogenesis of fatigue associated with liver disease. Specifically, experimental findings suggest that fatigue associated with liver disease likely occurs as a result of changes in neurotransmission within the brain. In conclusion, a reasonable approach to help guide the management of the fatigued patient with liver disease is presented.

Key Words: Cholestasis; Fatigue; Hepatitis; Liver disease; Neurotransmitters; Therapy

Fatigue is a complex symptom that encompasses a range of complaints including lethargy, malaise, lassitude and exhaustion. Chronic fatigue commonly occurs, affecting up to 20% of the population (1). Although the exact prevalence of fatigue in patients with chronic liver disease is somewhat variable in different studies and with different specific liver diseases, it is readily apparent that fatigue constitutes the most common complaint among this patient group (2-6). However, because of difficulties in defining and treating fatigue, this symptom is often overlooked or minimized by physicians caring for patients with liver disease. The prevalence of fatigue in patients with different forms of liver disease also appears to be quite variable. Specifically, cholestatic liver disease caused by primary biliary cirrhosis (PBC), primary sclerosing cholangitis or drugs is commonly associated with fatigue (2,3). In fact, fatigue in cholestatic patients can be the presenting symptom and occurs in 65% to 85% of patients (2,3,7,8). Moreover, fatigue in PBC is considered to be the worst symptom in approximately 50% of patients, and is disabling in approximately 25% (7). Fatigue also has a significant impact on the health-related quality of life (HRQOL) of PBC patients (7-9).

The prevalence of fatigue in hepatic liver diseases is less clearly defined. Fatigue is an integral component of the clinical presentation of patients with autoimmune hepatitis, often paralleling hepatic inflammation as determined by serum alanine aminotransferase measurements or liver biopsy findings, and responding usually quite rapidly to the institution of immunosuppressive therapy (4,10,11). However, the overall prevalence of fatigue in patients with viral hepatitis is less clear. Acute presentations of viral hepatitis are often associated with feelings of fatigue or malaise, which gradually subside because the patient recovers clinically (eg, recovers from hepatitis A). However, the situation in patients with chronic viral hepatitis appears to be more controversial. Specifically, a significant proportion of patients with chronic hepatitis C who are followed in tertiary care centres, or who participate in clinical trials, complain of fatigue or decreased vitality, which has a direct negative impact on their HRQOL (5,6,12). However, this high prevalence of fatigue does not appear to hold for patients infected with hepatitis C who are unaware of their diagnosis (13,14). Moreover, the complaint of fatigue in hepatitis C patients does not appear to correlate with whether these patients are viremic (15). In contrast, patients chronically infected with hepatitis B appear to have HRQOL scores similar to those of healthy controls (12).

Recently, patients with hepatitis C have been reported to have subclinical findings of cognitive impairment and altered cerebral metabolism as reflected by magnetic resonance spectroscopy (16-18). The suggestion from these findings is that hepatitis C infection of the brain itself may lead to these changes (17,19). However, it is unclear whether these central changes observed in hepatitis C-infected patients are a direct...
result of the hepatitis C virus within the brain, are related to the complex behavioural, social and mental sequelae associated with carrying a diagnosis of chronic hepatitis C infection or are related to the mode of acquisition of their hepatitis C (eg, intravenous drug abuse).

Therefore, any discussion of the pathophysiology and management of fatigue in the context of liver disease must take these observations into account.

**TYPES OF FATIGUE**

In any discussion of fatigue, it is imperative to differentiate central from peripheral fatigue. Peripheral fatigue relates to neuromuscular dysfunction and occurs with muscle overutilization and associated metabolic changes, and is classically manifested clinically by weakness (20,21). This type of fatigue does not appear to be important in patients with liver disease in the absence of decompensated cirrhosis or liver failure. In contrast, central fatigue arises within the central nervous system (CNS) and is characterized by a difficulty in performing physical (and often mental) activities, which require self-motivation and responses to internal cues. Furthermore, central fatigue is often associated with a higher perceived effort when undertaking tasks (20). Therefore, by definition, central fatigue directly results from altered neurotransmission within the brain.

Typically, the complaint of central fatigue in the setting of any chronic disease, including liver diseases, does not correlate with traditional markers of disease activity or severity (20,21). Moreover, central fatigue is often associated with other neuropsychiatric complaints also thought to be secondary to altered neurotransmission within the CNS; namely depression and anxiety (20,21). This association of fatigue with depression and anxiety is commonly encountered in patients with cholestatic and hepatitic liver diseases (6-8,22).

Given that central fatigue arises from changes in neurotransmitter systems within the brain, it is readily apparent that objective measurements of fatigue are problematic. Therefore, fatigue assessments in patients with liver disease have traditionally been performed using either general or specifically designed questionnaires (eg, Short Form-36 [12,15] versus Fatigue Impact Scale [23] or Fatigue Severity Scale [24]). By scoring a patient’s answers to a given set of questions concerning fatigue, these questionnaires allow for an objective quantification or score of fatigue to be made. Changes in these scores have been used to determine worsening or improving in fatigue with therapeutic interventions in patients with liver disease.

**PATHOPHYSIOLOGY OF FATIGUE IN LIVER DISEASE**

The pathogenesis of fatigue in general is poorly understood and this holds true for fatigue in the setting of liver disease (20,21,25). However, given that altered neurotransmission within the CNS drives central fatigue, and that central fatigue is the predominant issue in the setting of liver disease, any discussion of the possible etiology of fatigue in the context of liver disease must relate to these potential changes in neurotransmission within the brain (21,25,26). Therefore, the discussion of the pathophysiology of fatigue in liver disease must incorporate two main concepts:

1. How does the diseased or damaged liver ‘communicate’ with the brain to cause changes in neurotransmission?

2. What specific changes in neurotransmission occur within the brain as a result of this ‘communication’, and how do these changes give rise to the genesis of central fatigue?

Moreover, this discussion must also be placed in the context that fatigue in patients with liver disease is manifest in the setting of a diagnosis often holding an uncertain outcome and often associated with societal taboos. Therefore, the diagnosis of chronic liver disease encompasses complex interactions among biological, psychosocial and behavioural processes, which can all significantly affect the clinical expression of fatigue in a given patient.

As outlined previously, the ultimate cause of central fatigue in patients with liver disease must entail alterations in neurotransmitter pathways within the brain. The specific neurotransmitter pathways that have received the greatest clinical and experimental attention as potentially causing central fatigue include pathways that are important in behavioural activation, arousal and locomotor activity (25-28). Brain areas important in this regard include the basal ganglia, brainstem, reticular and limbic systems and higher cortical centres (20,25,26). The neurotransmitter systems that have been directly implicated in the genesis of central fatigue include the corticotropin-releasing hormone (CRH), serotonin, noradrenaline and other neurotransmitter systems.

**CRH**

CRH was initially identified as the factor released from the hypothalamus, which is the most potent activator of the hypothalamic-pituitary-adrenal axis. However, over the past three decades, it has become increasingly clear that CRH-containing nerve fibres are widely distributed throughout the CNS and are intimately involved in arousal and behavioural activation (27,29-31; Figure 1). These observations have led to

![Figure 1](image-url)
the hypothesis that defective release of CRH within the brain may be important in the development of central fatigue (31-33). In an animal model of cholestatic liver disease, behaviours and physiological responses consistent with defective central CRH release have been documented (34-36). In addition, rats with experimental cholestasis demonstrate reduced hypothalamic CRH levels and increased CRH type 1 receptor expression, as well as enhanced sensitivity to the behavioural activating effects of centrally infused CRH (36); these findings are consistent with defective central CRH release playing an important role in cholestasis-associated fatigue. Moreover, clinical observations in patients with PBC also support this suggestion. Specifically, PBC patients demonstrate augmented adrenocorticotropic hormone release after intravenous CRH infusion, consistent with an upregulation of pituitary CRH receptors in these patients, possibly secondary to defective endogenous CRH stimulation of their anterior pituitary glands (37). Of interest, defective central CRH release has also been implicated in central fatigue in patients with atypical depression and the chronic fatigue syndrome (26,32).

Serotonin
Abnormal serotonergic neurotransmission has been commonly implicated in the development of altered behaviours including depression, anxiety and central fatigue (28). Serotoninergic nerve fibres arise mainly within the dorsal raphe nucleus in the midbrain and project widely throughout the CNS (28,38,39). Of interest, the serotonin and CRH neurotransmitter systems are known to be intimately interrelated (38,40). Serotonin mediates its biological effects by activating a large number of receptor subtypes (41). However, the precise role played by serotonin in the generation of central fatigue remains unclear. It appears that serotonin released within the brain has a differential effect on the development of fatigue depending on whether exercise-induced fatigue or more classically defined central fatigue is being examined. Specifically, in rodents or athletes exercised to exhaustion, increased central serotonin levels appear to decrease exercise capacity (42,43). These observations suggest that increased central serotonin levels may contribute to central fatigue. However, the applicability of findings regarding serotonin in the setting of exercise to exhaustion appears to be less relevant to fatigue in the setting of liver disease. Patients with chronic fatigue syndrome exhibit findings on pharmacological challenge that are consistent with increased central serotonin sensitivity due to decreased serotonergic neurotransmission (44). These observations provided the impetus to use serotonin reuptake inhibitors to treat patients with chronic fatigue syndrome, albeit with mixed results (45).

The serotonin neurotransmitter system has been studied in an animal model of cholestatic liver disease and the findings are consistent with a possible role of serotonin in liver disease-associated fatigue (46,47). The 5-hydroxytryptamine (5HT)1A receptor subtype has been commonly linked to altered behaviours in humans and animals (48,49). The 5HT1A receptor exists as an autoreceptor situated on cell bodies of serotonergic nerves originating in the midbrain dorsal raphe nucleus (50; Figure 2). Activation of these cell body serotonin autoreceptors in the midbrain results in decreased serotonin release from the distal nerve terminals that project throughout the CNS (48-50). However, 5HT1A receptors also exist postsynaptically within the brain. Activation of postsynaptic 5HT1A receptors typically exerts an inhibiting influence on neurons where they are located (48). Therefore, systemic administrations of a 5HT1A receptor agonist results in a net decrease in serotonin neurotransmission at all postsynaptic serotonin receptors except those of the 5HT1A subtype (48). Experimental results in cholestatic rats are consistent with increased sensitivity and the number of 5HT1A midbrain autoreceptors coupled with normal 5HT1A postsynaptic receptors elsewhere within the CNS (46,47); these findings that would be expected to give rise to decreased central serotonin release as a potential contributor to central fatigue in cholestatic liver disease. In fact, this suggestion is supported by findings that the repeated administration of a 5HT1A receptor agonist, which desensitizes 5HT1A autoreceptors and increases central serotonin release into synapses where postsynaptic 5HT1A receptors are active, ameliorated fatigue-like behaviours in cholestatic rats (51). These observations suggest that the 5HT1A receptor may play an important role in the genesis of central fatigue in patients with liver disease.

More recently, 5HT3 receptor antagonists have been reported to improve fatigue in patients with the chronic fatigue syndrome (52), as well as in a patient with hepatitis C-induced fatigue (53). Similar findings have been reported in preliminary experiments in cholestatic rats (54). Of note, in a recent clinical trial, the 5HT3 receptor antagonist ondansetron appeared to have a limited effect on fatigue in PBC patients, although the results of this study are difficult to interpret due to possible patient unblinding and a significant placebo effect (55). Therefore, the role played by serotonin-activating central 5HT3 receptors in the genesis of liver disease-associated fatigue remains unclear.

Noradrenaline
Noradrenaline is a classical neurotransmitter important in behavioural activation, especially in the context of acute stress (56). More important, hypofunctioning of noradrenaline-containing nerve pathways within the brain has been implicated in the development of central fatigue (57). Specifically, reserpine, which depletes central calecholamine stores, is commonly associated with the development of fatigue and depression (58). Moreover, beta-blockers and alpha-2 agonists frequently cause increased sensitivity and the number of 5HT1A midbrain autoreceptors coupled with normal 5HT1A postsynaptic receptors elsewhere within the CNS (46,47); these findings that would be expected to give rise to decreased central serotonin release as a potential contributor to central fatigue in cholestatic liver disease. In fact, this suggestion is supported by findings that the repeated administration of a 5HT1A receptor agonist, which desensitizes 5HT1A autoreceptors and increases central serotonin release into synapses where postsynaptic 5HT1A receptors are active, ameliorated fatigue-like behaviours in cholestatic rats (51). These observations suggest that the 5HT1A receptor may play an important role in the genesis of central fatigue in patients with liver disease.
development of central fatigue in patients who are aware of
relates to disease-labelling may contribute significantly to the
self-worth and fear. Certainly this ‘indirect’ pathway that
involves social and professional interactions, and feelings of
sis of liver disease can be substantial because it directly
or liver failure, the psychological impact of carrying a diagno-
psychological stressor. Although the physical stress of chronic
chronic liver disease can be viewed as both a physical and a
regards to the genesis of central fatigue (65,66). Furthermore,
emissions within the brain, which have been discussed earlier with
rodents can induce marked changes in neurotransmitter sys-
tems (63,65,66). Of note, chronic stress in
human stressors as variceal bleed prophylaxis (59).

Other neurotransmitters
Numerous other neurotransmitter systems have also been
implicated in the control of locomotor activity and behavioural
activation, including the dopaminergic and cannabinoid sys-
tems (60,61). However, no studies of the role of these neuro-
transmitter systems in liver disease-associated fatigue have been performed.

The obvious question that arises is, how do these alterations
in central neurotransmission, which lead to fatigue, come about in the setting of liver disease? Although the answer to
this question is still unclear, it likely involves specific commu-
nication pathways from the diseased liver to the brain, as well
as nonspecific effects of liver disease acting in the context of a
chronic stress for an individual (62).

Chronic stress can have profound behavioural effects (63). These changes in behaviour can include depression, anxiety and fatigue (63,64). Moreover, this effect can be caused by
physical, psychological or a combination of stressors, and these
stressors have been implicated in changes in central neuro-
transmitter systems (63,65,66). Of note, chronic stress in
rodents can induce marked changes in neurotransmitter sys-
tems within the brain, which have been discussed earlier with
regards to the genesis of central fatigue (65,66). Furthermore,
chronic liver disease can be viewed as both a physical and a
psychological stressor. Although the physical stress of chronic
liver disease is often relatively mild in the absence of cirrhosis
or liver failure, the psychological impact of carrying a diagnos-
is of liver disease can be substantial because it directly
involves social and professional interactions, and feelings of
self-worth and fear. Certainly this ‘indirect’ pathway that
relates to disease-labelling may contribute significantly to the
development of central fatigue in patients who are aware of
their diagnosis (14,67-69). However, this does not account for
the observation that a significant proportion of patients with
liver disease presents to doctors specifically complaining of
fatigue before a diagnosis of liver disease is made. Therefore, a
‘direct’ communication pathway between the liver and the
brain appears to play an important role in fatigue genesis in the
context of liver disease.

Traditionally, communication between the periphery (ie, outside the CNS) and the brain has been considered to
involve two potential pathways: neural (ie, nerve projections; Figure 3) and/or humoral (ie, substances contained within the
circulation; Figure 4) (70). In the setting of liver disease, either
or both pathways may be activated.

The liver and peritoneum are richly innervated with affer-
ent signals being carried to the brain in vagal and spinal nerve
projections (71,72). Activation of these nerves during inflam-
ation in rodents stimulates areas of the brain important in
regulating behavioural arousal and results in the development of
fatigue-like behaviours (73-75). Moreover, these effects can
be abolished by subdiaphragmatic vagotomy (76). However,
patients who have recurrent liver inflammation following liver
transplantation and therefore after complete hepatic denerva-
tion (eg, hepatic C, FBC) often continue to experience
fatigue (77,78). These observations suggest that neural projec-
tions from the liver to the brain are less likely to contribute signi-
ficantly to changes in CNS neurotransmitter systems that
give rise to central fatigue in the setting of liver disease.

Communication between the diseased liver and the brain
may also occur via mediators released into the circulation as a
result of hepatic injury. In this regard, cytokines present within the
circulation have received the greatest attention (79,80). Speci-
ically, the liver contains the largest population of fixed
macrophages in the body, which represents an important
source of cytokines found in the circulation (79,80). Moreover,
elevated circulating cytokine levels have commonly been doc-
umented in the setting of both cholestatic and hepatic liver
diseases (81-85). Furthermore, elevations in circulating

neurotransmission in liver disease-associated fatigue remains
completely unknown. However, an obvious patient population
that could be studied includes cirrhotic patients taking beta-
blockers as variceal bleed prophylaxis (59).

Figure 3) Neural transmission pathway for liver to brain signalling. Kupffer cells within the liver secrete proinflammatory mediators (eg, cytokines, prostaglandins) that activate vagal afferent nerves, which
innervate the liver. Nerve impulses are then carried to the nucleus tractus solitarius (NTS) within the brainstem, which acts as a relay centre for the transmission of these impulses to areas throughout the brain. Stimulation of vagal afferent nerves can thereby result in alterations in neurotransmitter systems within the brain, which may give rise to central
fatigue

Figure 4) Humoral transmission pathway for liver to brain signalling. Substances released within the circulation in the setting of liver disease (eg, cytokines, including tumour necrosis factor-alpha (TNFα) activate the cerebral endothelial cells that make up the blood-brain barrier. Activated cerebral endothelial cells then secrete secondary messengers (eg, nitric oxide, prostaglandin E2) into the brain parenchyma, which
induce changes in central neurotransmitter systems, which give rise to central fatigue
Fatigue in liver disease

Management of fatigue in patients with liver disease

General approach
Management of central fatigue associated with liver disease is complicated and hampered by a general lack of understanding of fatigue in general. Therefore, specific therapies are currently not available. However, many patients can benefit from a systematic approach. An important first step in this process is to rule out causes of fatigue that may be separate from the patient’s liver disease. While meeting with a patient, specific questions should be asked with regard to symptoms of hypothyroidism, sleep patterns, behaviours, exercise, caffeine and alcohol ingestion, and life stresses. Moreover, a loss of motivation and pleasure in things that a patient would normally enjoy (ie, anhedonia), loss of interest in social activities, early morning awakenings, feelings of guilt and thoughts of suicide are important clues to the presence of depression and need to be directly addressed, and therapy instituted or psychiatric referral considered (20). In addition, a complete review of a patient’s prescription medications (eg, beta-blockers, benzodiazepines, etc) as well as over-the-counter medications and health supplements should be undertaken. Finally, simple laboratory tests should be performed to exclude other possible causes of fatigue (eg, thyroid-stimulating hormone, calcium, creatinine, blood urea nitrogen, electrolytes, fasting blood sugar and magnesium).

Modifying behavioural components to fatigue
Significant central fatigue warrants lifestyle changes, which may include rest periods and reduced workloads (104,105). However, the maintenance of physical activity is of paramount importance. The natural inclination of patients with central fatigue is to decrease physical activity. However, decreased physical activity over time will lead to cardiovascular and muscular deconditioning, which then makes physical activity even more difficult (104,105). Therefore, all patients need to be counselled with regard to maintaining an appropriate level of activity. In addition, an increase in activity should be attempted through the institution of a graded exercise program (106).

In many patients with liver disease and central fatigue, the degree and perpetuation of fatigue may be directly related to and influenced by a complex interaction of physiological, emotional, cognitive, behavioural, and social factors (107). A patient’s thoughts and beliefs (ie, cognitions) may contribute significantly to the maintenance of certain illness behaviours, including fatigue (107,108). This concept has received the greatest attention in the setting of central fatigue related to chronic fatigue syndrome (107,108). The idea is that psychological processes not only drive deleterious behavioural patterns, but also directly increase the perception of fatigue (108). Moreover, cognitive behavioural therapy is the only therapy of proven efficacy for patients with chronic fatigue syndrome (109). Therefore, cognitive behaviour therapy needs to be examined as a potential therapeutic modality for fatigue in patients with liver disease. Subjective sleep disturbance is commonly associated with fatigue in patients with liver disease (8,110). Therefore, all fatigued liver disease patients need to be counselled with regard to proper sleep habits. However, any historical clues as to the presence of a specific sleep disorder (eg, sleep apnea) may direct the pursuit of formal sleep studies. In this vein, alcohol and caffeine should be limited. Moreover, any medications that may be contributing to fatigue should be discontinued if possible.

Pharmacological interventions
Specific pharmacological therapies directed at the physiological abnormalities that may underlie central fatigue in patients with liver disease are currently not available. Nonspecific CNS stimulants, including modafinil, have been used to treat central fatigue (111,112); however, their use in patients with liver disease and fatigue has not been reported but may warrant further investigation, especially for patients with severe fatigue. Some patients respond to nocturnal therapy with low-dose amitriptyline, especially if poor sleep patterns are possibly contributing.

Conclusions
Fatigue is the most common symptom reported by patients with liver disease. Although the underlying pathogenesis of fatigue in liver disease is still poorly defined, it appears to involve changes in central neurotransmission, which result from signalling between the diseased liver and the brain. A
better understanding of the pathways and the neurotransmitter systems involved may provide directed specific therapies for liver disease-associated fatigue.

ACKNOWLEDGEMENTS: Mark G Swain is an Alberta Heritage Foundation for Medical Research Senior Scholar and a Canadian Institutes of Health Research Investigator.

REFERENCES


Swain