Although fatigue is the most common complaints reported by patients in primary care [1], last decades of research have been hampered by the lack of an objective measurement of the subjective experience of fatigue. The Fatigue Impact Scale (FIS) questionnaire was developed in 1994 by Fisk and colleagues to quantify the specific impact of fatigue on quality of life [2]. In Hepatogastroenterology, this validated tool has confirmed the disabling effect of fatigue in many chronic illness such as chronic hepatitis C [3, 4] and primary biliary cirrhosis [5, 6] but also in functional bowel disorders namely the irritable bowel syndrome (personal data). For instance, the FIS questionnaire is of particular interest in ongoing trials aimed at reducing fatigue. Considering the high prevalence of fatigue, thus inducing a considerable burden to the health care system, the elucidation of its still poorly known pathogenesis and the development of effective therapies for its relief are important goals for research in Hepatogastroenterology.

Physiopathology

Ten years ago, Swain and Maric [7] have proposed three theories based on findings in a rat model, that considered central incompetence or variations thereof as a critical issue in the pathogenesis of fatigue: (i) neuroendocrine causes, with abnormal function of the hypothalamic-pituitary-adrenal axis; (ii) alterations in immune activation and cytokines release (e.g. proinflammatory cytokines); and (iii) abnormalities in neurotransmission, particularly in the central serotonin pathway. Whether the disturbances of the hypothalamic-pituitary-adrenal axis observed by some authors, but not all, are of functional importance remain controversial (for review [8]). To date, there is growing evidence that the central component of fatigue associated with chronic conditions plays a key role compared to peripheral mechanisms. Subsequent studies in animals and humans have confirmed the importance of alterations within the brain stem, in the chronic fatigue syndrome [9, 10], cholestatic liver diseases [11] or chronic hepatitis C [12, 13]. The recognition of altered neurotransmission has also brought the possibility of pharmacological manipulation of receptors and transmitters, especially serotonin (5-HT), opioid, and substance P (e.g. substances that can influence behavior in both animals and humans). Moreover, the key role of immunity has recently been enlightened and high circulating leptin and TNF-α (i.e. proinflammatory cytokines) levels have been associated with the severity of fatigue in patients with chronic hepatitis C [3] or irritable bowel syndrome (personal data). Nevertheless, the pathogenesis of fatigue probably does not lend itself to this reductionist thinking and given the many confounding factors that may impinge on behavior, it is likely that fatigue is mediated through a more complex dysfunction of the central nervous system, neurotransmission, immunity, endocrine factors and micronutrients which may be altered at various degrees depending of the underlying disease.

What are the ways to improve fatigue in GI diseases?

Selective serotonin reuptake inhibitors and 5-HT receptor antagonists

Considering the altered neurotransmission, it is well established that the serotonin pathway is involved in both anxiety and depression and may participate to fatigue. Therefore, the drug class of selective serotonin reuptake inhibitors and 5-HT receptor antagonists have been evaluated to treat fatigue in many conditions with conflicting results. In an open study, it was shown that blockade of both 5HT2 and HT3 receptors with mirtazapine was associated with a 40 % or more reduced intensity of fibromyalgia symptoms, including fatigue, as well as reduced severity of depression [14]. In another study, fatigue was significantly and substantially reduced when patients with chronic fatigue were switched from placebo to 20 or 40 mg of the serotonin reuptake inhibitor citalopram [15]. However, the findings were less impressive in a design comparing the effect of citalopram and placebo after two months of treatment [15]. In patients with chronic fatigue, the oral administration of the 5-HT3 receptor antagonist ondansetron has also been shown to relieve fatigue [16]. Conversely, fatigue was not improved in a large cohort of 549 fatigued patients with cancer receiving chemotherapy who were randomly assigned to receive either 20 mg of oral selective serotonin reuptake inhibitor paroxetine hydrochloride daily or placebo for 8 weeks [17]. In chronic liver diseases, there is growing acceptance that cholestasis is associated with altered opioid and 5-HT mediated neuromodulation, which contributes to the pruritus of cholestasis [11]. It is noteworthy that 5-HT, like opioid agonists, modulates nociception in normal rats [18], and might also interfere with the perception of pruritus. This concept...
is supported by the fact that the intravenous administration of the selective 5-HT3 receptor antagonist ondansetron to patients with cholestatic liver diseases has been associated with acute improvement of pruritus [19]. Therefore, this drug class (e.g. serotonin reuptake inhibitors and 5-HT receptors antagonists) was used in several trials aimed at reducing fatigue associated with cholestasis. In a rat model, Swain et al. [20] have recently demonstrated that cholestasis was associated with increased central 5-HT3 receptor expression in a brain area implicated in behavioral activation. Moreover, in the same model, inhibition of 5-HT3 receptor activation was shown to improve cholestasis associated fatigue-like behavior [20]. In alcoholic dependant individuals, the selective 5-HT3 receptor antagonist ondansetron (16 µg/kg twice daily) has been shown to have a greater therapeutically efficacious effect at alleviating symptoms of overall mood disturbance, fatigue, vigor, confusion/bewilderment, and depression among early onset alcoholics compared with late-onset alcoholics [21]. Finally, a woman with chronic hepatitis C and profound fatigue has been reported to become symptom free when treated with long-term ondansetron 4 mg twice daily [22]. In the light of these findings, we were encouraged to perform a double blind randomized trial with this compound in a cohort of 36 patients with chronic hepatitis C and fatigue. In this study, patients did not receive any antiviral therapy and one month oral administration of the 5-HT receptor type 3 antagonist ondansetron (4 mg twice daily) induced a significant 30% improvement of the total score of fatigue measured with the FIS whereas placebo did not. Interestingly, this effect persisted one month after the treatment had been stopped [23]. In this study, ondansetron was also effective in diminishing the scores of the Beck Depression Inventory used to measure depression. Although the mechanism of this effect remains unclear, we have observed that circulating leptin levels were reduced in the group of patients receiving ondansetron but not in the placebo group (unpublished data). Further trials are warranted to confirm these findings because reducing fatigue may be of crucial importance to increase the observance of antiviral therapy in chronic hepatitis C. In the future, it may be possible to better target serotonin reuptake inhibitors in individuals rather than using the current trial, thus giving the possibility of a more specific central effect.

L-carnitine

Carnitine is a hydrophilic substance that plays a key role in the carriage of fatty acids from the cytosol into the mitochondria for oxidation and energy production [24]. It has been suggested that the administration of L-carnitine may enhance its intracellular level, while decreasing muscular weakness, low incidence of activity and also fatigue [25]. In an open label study, Cruciani et al. [26] have reported that 83% of patients with fatigue related cancer had carnitine deficiency and that a week of L-carnitine supplementation increased its plasma levels and relieved fatigue, depression and sleep disruption in a substantial proportion of patients. In a recent study, it has been shown that high serum carnitine values allow a better response to interferon therapy, enhancing compliance and reducing some side-effects [27]. The role of carnitine in the pathogenesis of fatigue is also supported by a recent study in the chronic fatigue syndrome in which patients with low serum carnitine levels had reduced gray-matter volume in the bilateral prefrontal cortex evaluated with magnetic resonance imaging [28]. Within these areas, the volume reduction in the right prefrontal cortex paralleled the severity of the fatigue of the subjects [28]. These data are consistent with previous reports of an abnormal acetyl-L-carnitine uptake in the prefrontal cortex, which is one of the biochemical markers of chronic fatigue syndrome.

Substance P and neurokinin-1 receptor antagonists

The neuropeptide substance P and its receptor, the neurokinin-1 receptor (NK1), have been implicated in the pathophysiology of affective disorders, including depression and anxiety. Haddjeri et al. [29] have shown that, as occurs with other major types of antidepressants, substance P antagonists might alleviate anxiety and major depression, in part, by enhancing the levels of some 5-HT receptors in the forebrain. Moreover, it was demonstrated in animals that interactions between NK1 and 5HT1A receptors within the dorsal raphe nucleus neural networks may contribute to the mechanism of action of novel antidepressants acting at NK1 receptors [30]. Although the effect of NK1 antagonists on fatigue is unknown, it is tempting to speculate that these compounds may relieve fatigue. This concept may be of crucial importance, especially in patients with irritable bowel syndrome (personal data) [31] or inflammatory bowel disease [32] in whom fatigue is a frequent non gastrointestinal complaint. For instance, these compounds are currently under development in irritable bowel syndrome patients because TAK-637, a new NK1 receptor antagonist, has been shown to play an important role in stress-induced changes in colonic function in vivo [33].

Conclusion

From the data evaluated so far, there is evidence that 5-HT3 receptor antagonists provide significant benefit in a substantial proportion of patients with chronic hepatitis C and fatigue. In clinical practice, our data justify a careful application with appropriate dosage to avoid adverse reaction (e.g. constipation). The duration of therapy still remains to be further explored. In addition, the recent reported adverse events from therapy of irritable bowel syndrome with alsereton provide a note for caution before a widespread use of such compounds to treat fatigue. Future development of more effective agents will depend both on a better understanding of the neural pathways and receptors involved in the control of fatigue, as well as on the investigation of new more selectively targeted compounds. At present, the treatment of fatigue in Hepatogastroenterology must be regarded at the threshold of transition from concept to well designed clinical studies.

REFERENCES


ABBREVIATIONS:
FIS : fatigue impact scale
NK1 : neurokinin 1


