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Association of a deficit of arousal with fatigue in multiple sclerosis: Effect of modafinil

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ABSTRACT

Multiple sclerosis (MS) is a multifocal demyelinating disease of the central nervous system, leading to chronic disability. Fatigue is a common and distressing symptom of MS which is unrelated to its clinical form, stage of development, the degree of disability, or the lesion load on magnetic resonance imaging. Fatigue in MS is associated with excessive daytime sleepiness and autonomic dysfunction. Recently it has been reported that the wakefulness-promoting drug modafinil may relieve fatigue in MS patients and ameliorate the associated cognitive difficulties. However, it is not clear to what extent the anti-fatigue effect of modafinil may be related to its alerting and sympathetic activating effects. We addressed this question by comparing three groups of subjects, MS patients with fatigue, MS patients without fatigue and healthy controls, matched for age and sex, on measures of alertness (self-ratings on the Epworth and Stanford Sleepiness Scales and on a battery of visual analogue scales; critical flicker fusion frequency; Pupillographic Sleepiness Test; choice reaction time) and autonomic function (systolic and diastolic blood pressure, heart rate, pupil diameter), and by examining the effect of a single dose (200 mg) of modafinil on these measures. MS patients with fatigue, compared with healthy controls, had reduced level of alertness on all the tests used; MS patients without fatigue did not differ from healthy controls. MS patients with fatigue had a reduced level of cardiovascular sympathetic activation compared to the other two groups. Modafinil displayed alerting and sympathomimetic effects in all three groups of subjects. As fatigue in MS is associated with reduced levels of alertness and sympathetic activity, modafinil may exert its anti-fatigue effect in MS by correcting these deficiencies. The anti-fatigue effect of modafinil may reflect the activation of the noradrenergic locus coeruleus (LC), since there is evidence that this wakefulness-promoting nucleus is damaged in MS, and that modafinil, probably via the dopaminergic system, can stimulate the LC.

This article is part of a Special Issue entitled 'Cognitive Enhancers'.

1. Introduction

Multiple sclerosis (MS) is a multifocal demyelinating disease of the central nervous system, leading to chronic disability. Its course can be relapsing/remitting in the majority of patients. However, a relapsing/remitting course often assumes later a progressively deteriorating course (secondary progressive MS), or the course can be progressive from the onset (primary progressive MS) (Lublin and Reingold, 1996).

Fatigue is a common symptom of MS irrespective of its clinical form (Krupp et al., 1988; Bakshi, 2003; MacAllister and Krupp, 2005). Fatigue in MS is also unrelated to the degree of physical disability or to lesion load on conventional magnetic resonance imaging (Racke et al., 2004). Fatigue has been defined as "subjective lack of physical and/or mental energy that is perceived to interfere with usual and desired activities" (Tartaglia et al., 2004). MS patients rate fatigue as one of their worst symptoms, interfering with their quality of life and leading to disability (Krupp et al., 1988, 1989; Janardhan and Bakshi, 2002). A number of clinical scales have been developed for the measurement of fatigue in MS, such as the Fatigue Severity Scale (FSS) (Krupp et al., 1989), which is part of the Fatigue Assessment Instrument (FAI) (Schwartz et al., 1993),

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the Fatigue Impact Scale (FIS) (Fisk et al., 1994), the Modified Fatigue Impact Scale (MFIS) (Fisk and Doble, 2002) and the Neurological Fatigue Index (NFI-MS) (Mills et al., 2010). Only a weak correlation has been found between different rating scales, suggesting that "fatigue is a multidimensional symptom and therefore the available tests measure and weight different aspects of fatigue" (Flachenecker et al., 2002).

It has been reported that fatigue in MS may be associated with increased sleepiness. The relationship between fatigue and sleepiness is complex, and some patients may report tiredness (or fatigue) when they mean "increased need for sleep" (Dement et al., 2003). The term "tiredness" may be used as euphemism for "sleepiness": the warning on British motorways "Take a break! Tiredness kills!" means "Take a break! Sleepiness kills!". There is evidence of sleep disturbance in MS (Attarian et al., 2004; Kaynak et al., 2006; Brass et al., 2010; Constantinescu et al., 2011; Kaminska et al., 2011) which has been implicated in the fatigue reported by the patients (Kaminska et al., 2011). Disrupted night time sleep may lead to excessive daytime sleepiness (EDS). Indeed, a correlation has been demonstrated between the scores obtained on sleepiness and fatigue rating scales in MS patients with fatigue (Attarian et al., 2004).

As there is a close association between the level of arousal and autonomic activity (Samuels and Szabadi, 2008), it is of interest that MS patients may also show disturbance of autonomic functions (Elie and Louboutin, 1995; McDougall and McLeod, 2003; Sanya et al., 2005; Haensch and Jörg, 2006; Merkelbach et al., 2006). Furthermore, Flachenecker et al. (2003) found an association between fatigue in MS and sympathetic vasomotor dysfunction. Interestingly, autonomic dysfunction has also been reported in other conditions, such as chronic fatigue syndrome, characterized by pathological fatigue (Newton et al., 2007).

Treatment of fatigue in MS is difficult (Zifko, 2004). Recently, there has been an interest in the wakefulness-promoting drug modafinil (Ballon and Feifel, 2006; Minzenberg and Carter, 2008) as a possible treatment for MS fatigue. A number of open label studies (Zifko et al., 2002; Nagels et al., 2007; Wilken et al., 2008; Brioschi et al., 2009; Lange et al., 2009; Littleton et al., 2010) and one placebo-controlled trial (Rammohan et al., 2002) have found that modafinil was efficacious in relieving fatigue in MS patients; although this was not confirmed in two placebo-controlled trials (Stankoff et al., 2005; Möller et al., 2011).

Apart from fatigue, cognitive impairment is also a common clinical feature of MS (Bobholz and Rao, 2003; Rao, 2004). Interestingly, the subjective experience of fatigue is often associated with both subjective cognitive difficulties and demonstrable cognitive impairment, and it has been reported that modafinil may be effective in relieving not only the fatigue but also the associated cognitive deficits in MS patients (Wilken et al., 2008).

It is not clear in what way modafinil may alleviate fatigue in MS patients. It is well documented that modafinil increases the level of alertness (Hou et al., 2005; Minzenberg and Carter, 2008), and there is also evidence that the increase in alertness is accompanied by the activation of the sympathetic nervous system (Taneja et al., 2005; Hou et al., 2005). Therefore, it is possible that the beneficial effect of modafinil on fatigue in MS patients is due to the alleviation of some symptoms (sleepiness, sympathetic dysfunction) associated with fatigue rather than to the relief of fatigue per se.

In the present study, in an attempt to explore the relationship between the anti-fatigue and alerting/sympathomimetic effects of modafinil, we examined whether there is any difference between MS patients with fatigue, MS patients without fatigue, and healthy controls on measures of alertness and autonomic function. We also examined the hypothesis that MS patients with fatigue may be more sensitive to the alerting and sympathetic activating effects of modafinil than MS patients without fatigue or healthy subjects. Therefore we compared the effects of a single dose (200 mg) of modafinil and placebo on measures of alertness and autonomic function in the three groups of subjects.

Some of the results have been presented to the British Association for Psychopharmacology, and published in abstract form (Szabadi et al., 2008, 2009).

2. Material and methods

2.1. Subjects

Three groups of subjects (MS patients with fatigue, MS patient without fatigue, healthy controls), matched for age and sex, were studied (Table 1).

2.1.1. Patients

Twenty-six patients with MS, as defined by the criteria of McDonald et al. (2001), were recruited. The group distribution by clinical type of the disease was: 21 relapsing-remitting MS (RRMS), 3 secondary progressive MS (SPMS) and 2 primary progressive MS (PPMS). There were 9 males and 17 females. All subjects were relapse- and corticosteroid-free for at least one month prior to commencement of the study as well as for the duration of the study. No patients suffered from any significant medical or psychiatric conditions that could confound the study. No patients had evidence of prior ocular manifestations of MS or impaired visual function, as assessed by the Visual Function Questionnaire VFQ25 (Noble et al., 2006).

As there can be an association between fatigue and depression (Goodwin, 1998), all patients were asked to complete the Beck Depression Inventory (BDI; Beck et al., 1996) prior to inclusion in the study. All patients included had BDI scores <19 (a cut-off to indicate no or mild depression).

All patients were divided into two groups according to severity of fatigue, based on their scores obtained on the Fatigue Severity Scale (FSS; Krupp et al., 1989). It is generally accepted that a score ≥ 5.0 qualifies for "fatigue", whereas a score of ≤ 4.0 qualifies for "no fatigue" (Bakshi et al., 2000; Andreasen et al., 2009). In our sample 16 patients had FSS in excess of 5.0 and thus fulfilled the criterion for "fatigue" (F) (Group 1). 9 patients had FSS scores less than 4.0 and thus fulfilled the criterion for "no fatigue" (NF) (Group 2). One patient had a borderline score between 4.1 and 4.9 and this patient was included in the fatigue group (Table 1). No patients with fatigue were receiving medication that could potentially affect their fatigue. Three patients in each group were receiving glatiramer acetate treatment and one patient in the NF group was receiving intramuscular beta-interferon.

2.1.2. Healthy controls

9 healthy control subjects were recruited to match with the patients for age and gender (Group 3). None of them had a history of neurological and/or psychiatric disease or other significant medical condition.

Approval was obtained from the Nottingham Research Ethics Committee. All subjects gave informed consent.

2.2. Drugs

Single doses of modafinil (200 mg) and lactose placebo were administered in matching capsules.

2.3. Design

Each subject participated in an initial introductory session and two experimental sessions, two weeks apart. In the experimental session the subjects were allocated to treatment according to a double-blind balanced cross-over design.

2.4. Procedure

In the introductory session the subjects completed the fatigue and depression questionnaires, and underwent a full neurological examination by an experienced clinician. The time-course of the experimental sessions was based on the single-

Table 1
Characteristics of the subjects.

	Number		Age (year)	FSS scores
	Male	Female	Mean ± SD	
Group 1[a] fatigue patients	5	12	49.4 ± 9.2	>4.1
Group 2[b] non-fatigue patients	4	5	41.8 ± 13.1	<2.9
Group 3 healthy controls	4	5	40.6 ± 12.1	

[a] 14 relapsing-remitting MS + 3 progressive MS.
[b] 8 relapsing-remitting MS +1 progressive MS.