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Norepinephrine and epinephrine responses to physiological and pharmacological stimulation in chronic fatigue syndrome

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ABSTRACT

Chronic fatigue syndrome (CFS) is characterized by fatigue lasting 6 months or longer. CFS has been associated with a disturbed (re-)activity of the autonomic nervous system. However, the sympathetic adrenomedulla (SAM) remains under-examined in CFS. To investigate SAM reactivity, we implemented a submaximal cycle ergometry (ERGO) and a pharmacological test (Insulin Tolerance Test, ITT) in 21 CFS patients and 20 age-, sex-, and BMI-matched controls. Plasma norepinephrine and epinephrine were collected once before and twice after the tests (+10/+20, and +30 min). Lower baseline levels and attenuated responses of epinephrine to the ERGO were found in CFS patients compared to controls, while the groups did not differ in their responses to the ITT. To conclude, we found evidence of altered sympathetic-neural and SAM reactivity in CFS. Exercise stress revealed a subtle catecholaminergic hyporeactivity in CFS patients. It is conceivable that inadequate catecholaminergic responses to physical exertion might contribute to CFS symptoms.

1. Introduction

Chronic fatigue syndrome (CFS) refers to fatigue of more than 6 months duration that cannot be sufficiently explained by any medical or psychiatric condition. According to the Centers for Disease Control and Prevention (CDC) 1994 diagnostic criteria, a number of ancillary symptoms, such as myalgia, memory and concentration problems, and postexertional malaise need to be fulfilled for a diagnosis of CFS (Fukuda et al., 1994). The diagnosis of CFS requires a complete clinical evaluation to exclude any medical or psychiatric cause of symptoms. Prevalence rates range from 0.2% to 2.5% in the general population, with women being more frequently affected than men (Reeves et al., 2007; Reyes et al., 2003). CFS provokes substantial suffering and impairment in patients (Lowry & Pakenham, 2008), leading to a considerable amount of direct (e.g., medical care) and indirect (e.g., lost productivity) costs for society (Lin et al., 2011).

Elucidating pathophysiological mechanisms in any illness is important in identifying targets for treatment. Given the heterogeneity and complexity of CFS, the identification of underlying psychological and physiological mechanisms is still subject to extensive research. A prominent line of research has been dedicated to the role of stress as an etiological and perpetuating factor in CFS (Nater, Fischer, & Ehlert, 2011). On a physiological level, stressors might result in a deregulation of stress-responsive systems, such as the hypothalamic–pituitary–adrenal axis (HPA), the autonomic nervous system (ANS), and the immune system (Danese, Pariante, Caspi, Taylor, & Poulton, 2007; Evans & English, 2002; Heim et al., 2000). It has been suggested that this deregulation contributes to core symptoms of CFS, such as pain and fatigue (Fries, Hesse, Hellhammer, & Hellhammer, 2005; Irwin, 2011; Rief & Barsky, 2005). In accordance with these propositions, symptoms of CFS are exacerbated by psychological (e.g., life events; Lutgendorf et al., 1995) and physiological stress (e.g., exercise; Jammes, Steinberg, Mambrini, Bregeon, & Delliaux, 2005), possibly resulting in postexertional malaise and avoidance behavior often found in these patients (Nater et al., 2006; VanNess, Stevens, Bateman, Stiles, & Snell, 2010).

Due to the observation that conditions characterized by a dysfunctional ANS, such as neurally mediated hypotension or postural orthostatic tachycardia, share prominent clinical features with CFS (e.g., Rowe, Bou-Holaigah, Kan, & Calkins, 1995), several studies have investigated autonomic abnormalities in patients suffering from CFS, yielding inconsistent results (Nater, Heim, & Raison, 2012). Most of this research focused either on the sympathetic neural or the parasympathetic branch of the ANS using indirect measures of autonomic activity such as heart rate or heart rate

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variability. However, power spectrum analysis of heart rate variability as a measure of sympathetic activity is still considered equivocal in terms of the relative contributions of the sympathetic and parasympathetic nervous system (Task Force, 1996). Only few studies have been dedicated to the examination of the sympatho-adrenomedullary (SAM) part of the ANS (Boneva et al., 2007; De Lorenzo, Hargreaves, & Kakkar, 1997; Ottenweller, Sisto, McCarty, & Natelson, 2001; Streeten, Thomas, & Bell, 2000; Timmers et al., 2002), focusing on the release of the catecholamines epinephrine (E), and – to a lower extent (Goldstein, McCarthy, Polinsky, & Kopin, 1983) – norepinephrine (NE) from chromaffin cells in the adrenal medulla. This is somewhat surprising, since catecholamines are the main effectors of the sympathetic nervous system and the SAM system in particular and are therefore intimately related to stress-related pathophysiology (Kvetnansky, Sabban, & Palkovits, 2009). Studies merely assessing baseline levels of catecholamines reported no differences between adult CFS patients and controls (Boneva et al., 2007; De Lorenzo et al., 1997). However, subtle differences in catecholaminergic activity as well as the role of feedback mechanisms might only be revealed during challenges. Three studies employed physiological challenges with adult CFS patients (Ottenweller et al., 2001; Streeten et al., 2000; Timmers et al., 2002), of which two tested the effects of orthostatic stress. Unfortunately, these tests are limited in their ability to elicit both NE and E responses concomitantly (Robertson et al., 1979).

Exercise, on the other hand, increases both sympathetic neural and adrenomedullary activity. In addition, this test bears the advantage of being a critical real-life stressor in CFS and might possibly be related to post-exertional malaise and avoidance behavior in these patients (Jammes et al., 2005; VanNess et al., 2010). A number of studies have used an exercise protocol to test physiological capacity und cardiac function in CFS in the laboratory, yielding inconsistent findings (Gibson, Carroll, Clague, & Edwards, 1993; Montague, Marrie, Klassen, Bewick, & Horacek, 1989; Riley, O'Brien, McCluskey, Bell, & Nicholls, 1990; Sisto et al., 1996; Wallman, Morton, Goodman, & Grove, 2004). However, exercise testing does not only allow for the assessment of physiological capacity but can also be used as a psycho-physiological stressor. This is due to the fact that exercise testing provokes intraindividual processes that might impact motivation and effort (Silver et al., 2002). There is only one published CFS study using (treadmill) exercise as a stressor to challenge the release of catecholamines, showing lower responses of E in CFS compared to healthy controls (Ottenweller et al., 2001). Nothing is known about catecholaminergic responses toward other exercise protocols, such as the frequently used cycle ergometry test (ERGO), in CFS patients.

A far more common approach to study endocrine stress responses involves the use of highly standardized pharmacological protocols. In contrast to exercise testing, these protocols offer an opportunity to minimize the effects of intraindividual processes. A frequently used pharmacological stressor to study the integrity of (hypoglycemia-responsive) endocrine systems in CFS is the Insulin-Tolerance-Test (ITT). The intravenous injection of insulin results in a marked hypoglycemia that provokes a counterregulatory response on the hypothalamic, pituitary and adrenal level, thus constituting a robust stimulus of adrenomedullary catecholamine release (Goldstein, 2010; Pacak, Baffi, Kvetnansky, Goldstein, & Palkovits, 1998). This test has previously been implemented in the study of endocrine dysfunction in CFS, eliciting normal or diminished HPA axis responses in these patients (Bearn et al., 1995; Gaab et al., 2004). Of note, this stimulus does not rely on cognitive-evaluative or affective processes to elicit an adaptive response and is therefore recommended in the study of adrenomedullary function. Currently, nothing is known about the ITT- or hypoglycemia-induced release of NE and E from the adrenal medulla in CFS.

In sum, deregulated stress–responsive systems seem to play a major role in the development and perpetuation of CFS. While there is evidence for a deregulation of the ANS in a subgroup of CFS patients little is known about a possible stress-related deregulation of catecholamines as direct effectors of the sympathetic-neural and SAM system. Moreover, previously used autonomic stress protocols did not show adequate relevance regarding CFS symptomatology.

The aims of this study are therefore to assess the responses of NE and E (outcome variables) to both the ERGO and ITT in male and female CFS patients compared to healthy controls (predictor variables). Employing these two tests will allow us to disentangle different aspects of stress-induced adaptive responses underlying a potentially deregulated stress reactivity in CFS, i.e., its physiological component (as elicited by the ITT) and intraindividual factors, such as cognitive-evaluative and affective processes. Based on the evidence mentioned above, we expect a relative hyporeactivity of both NE and E in CFS patients to the ERGO and the ITT. Due to cognitive-evaluative processes and the subsequent affective response to exercise, we expect that hyporeactivity is even more pronounced in the ERGO condition. In addition, investigating both men and women will enable us to explore sex-related differences in physiological alterations possibly underlying higher CFS prevalence rates in women.

2. Methods

2.1. Subjects

A total of 41 subjects participated in this study. Patients were contacted through a German self-help organization. Interested patients received a postal screening questionnaire, containing all symptoms required by the CDC 1994 definition (Fukuda et al., 1994). Patients fulfilling the symptom requirements in this screening questionnaire were interviewed over the phone and asked for diagnosed medical illnesses and psychiatric disorders. Interested patients were only excluded from participating in the study if they had received a medical or psychiatric diagnosis defined as exclusionary by the CDC 1994 definition (Fukuda et al., 1994). Further selection criteria were acute onset of CFS, between 30 and 50 years of age, no current antidepressive, anxiolytic, antibiotic, antihypertensive, or steroid medication and no medical or psychiatric cause for chronic fatigue using routine laboratory testing and psychiatric interviews. Thus, ten men and 13 women were selected from a cohort of 86 subjects with chronic fatigue syndrome willing to participate in the study. Patients were admitted to the research unit of a general hospital for the duration of one week. All patients were medically examined according to CDC recommendations (Fukuda et al., 1994), and interviewed by a trained psychologist (J.G.) using a computer-aided standardized diagnostic interview (Wittchen & Pfister, 1997) and a semi-structured CFS interview. Two female patients were excluded from the study due to hormone levels indicative of thyroid hypofunction and primary adrenal insufficiency, diagnosed by a blunted cortisol response to Synacthen (Ciba, Wehr, Germany). Patients were matched for age and sex with a total of 20 healthy volunteer controls. Controls were medication-free and underwent comprehensive medical examination for past and current health problems. All subjects provided written informed consent before participation in the study and ethical committee approval for the study was obtained. The study was conducted in accordance with the Declaration of Helsinki. Not all CFS patients underwent both tests; three female patients were unwilling to participate in the ITT, resulting in a sample of 18 patients undergoing the ITT test. Further, not all control subjects were included in both tests; seven controls (three men and four women) did not undergo the ITT. Therefore, four new control subjects (two men and two women) were recruited for this test, resulting in a sample of 17 control subjects participated in the ITT. The newly recruited control subjects did not differ in demographic variables and underwent the same screening and test procedures as the other control subjects while only undergoing the ITT. Patients and controls were not compensated for participating.

2.2. Test protocols

Each subject participated in two laboratory sessions. All subjects arrived 60 min before each test. They were taken into a separate room and an intravenous catheter was inserted and kept patent with a heparin lock. All subjects had to rest for at least 45 min. A baseline blood sample was collected immediately before the respective test began. After the incremental ERGO, starting at 1400 h, all subjects were taken back into their room for further sampling. Subjects who agreed to participate in the ITT reported to the laboratory 48 h after the ERGO. The ITT started at 0945 h. Blood samples for determination of NE and E responses were taken 10 and 30 min (ERGO) and 20 and 30 min (ITT) after the respective test.