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Orexin and sleep quality in anorexia nervosa: Clinical relevance and influence on treatment outcome

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ABSTRACT

Background and aims: Orexins/hypocretins are orexigenic peptides implicated in the regulation of feeding behavior and the sleep/wake cycle. Little is known about the functioning of these peptides in anorexia nervosa (AN). The aims of the current study were to evaluate the extent to which orexin-A might be linked to sleep and treatment outcome in AN.
Method: Fasting plasma orexin-A concentrations were measured in 48 females with AN at the start of a day hospital treatment and in 98 normal-eater/healthy-weight controls. The Pittsburgh Sleep Quality Index was administered at the beginning of the treatment as a measure of sleep quality. Other psychopathological variables were evaluated with the Symptom Checklist-Revised (SCL90R) and the Eating Disorder Inventory-2 (EDI). Patients were assessed at the start and end of treatment by means of commonly used diagnostic criteria and clinical questionnaires.
Results: The AN patients presented more sleep disturbances and poorer overall sleep quality than did the healthy controls ($p = .026$) but there were no global differences between groups in plasma orexin-A concentrations ($p = .071$). In the AN sample, orexin-A concentrations were associated with greater sleep disturbances ($|r| = .30$), sleep inefficiency ($|r| = .22$) and poorer overall sleep ($|r| = .22$). Structural Equation Modeling (SEM) showed that both elevated orexin-A concentrations and inadequate sleep predicted poorer treatment outcome.

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Conclusion: Plasma orexin-A concentrations contribute to poor sleep quality in AN, and both of these variables are associated with therapy response.

1. Introduction

Anorexia nervosa (AN) is a severe eating disorder (ED) particularly prevalent in adolescent girls and young women (Lucas et al., 1991, 1999; Hoek and van Hoeken, 2003; Hudson et al., 2007). AN is characterized by inappropriate eating behavior, an extreme pursuit of thinness, an intense fear of weight gain and a disturbance in body image (American Psychiatric Association, 2013). The syndrome yields numerous critical medical complications (Winston and Stafford, 2000; Do Carmo et al., 2007; Misra and Klibanski, 2014). Some studies report that, compared to healthy controls (HC), AN patients display sleep disturbances (Lauer and Krieg, 2004; Pieters et al., 2004; Kim et al., 2010), including reduced slow wave sleep (SWS) and REM sleep, shorter sleep duration and poor sleep efficiency (Benca et al., 1992; Nobili et al., 1999; Marca et al., 2004; Kim et al., 2010). Other studies have failed to find sleep-related disturbances in AN (Lauer et al., 1988, 1990). Inconsistencies may be due to heterogeneity of patient samples and methodological differences across studies (Lauer and Krieg, 2004).

Some studies have linked sleep disturbances in AN to low body mass index (BMI) (Della Marca et al., 2004) and malnutrition (Delvenne et al., 1996). Malnutrition is known to have damaging effects in the functioning of several neurological networks, including some involved in sleep behavior. For example, reduced connectivity strength and an increase in the characteristic path length of the thalamus have been identified in AN (Geisler et al., 2015). Additionally, thalamocortical circuitry is believed to play an important role in the regulation of sleep oscillations (Tsai et al., 2010). Another factor that might be implicated in the sleep disturbances reported by AN regards the clinical characteristics of eating disorders (e.g. drive for thinness, bulimic episodes and impulse regulation). Patients with ED who have sleep disturbances present more severe ED symptoms, such as drive for thinness and impulse regulation (Kim et al., 2010). Similarly, college students identified as having severely disturbed eating habits have also been found to sleep less than those with a more realistic body image (Makino et al., 2006).

Animal studies exploring the link between food deprivation and sleep have implicated nutrition-linked changes in plasma orexin (OX) concentrations (Lauer and Krieg, 2004; Ohno and Sakurai, 2008). OXs/hypocretins, consisting of orexin-A (OXA) and -B (OXB), are 33- and 28- amino acid neuropeptides expressed in the lateral hypothalamic area (Sakurai et al., 1998). Situated downstream from the leptin regulatory pathway, OXs are believed to act as orexigenic peptides that signal hunger in response to limited food availability (Sakurai et al., 1998). Food restriction has been found to augment OXA expression in rodents (Pankevich et al., 2010). Fasting in non-obese humans results in a gradual increase in serum OXA, which normalizes with re-feeding (Komaki et al., 2001). In addition, OXs seem to be involved in the sleep/wake cycle, promoting wakefulness and arousal (Tsujino and Sakurai, 2013). Injection of OX has an overall stimulatory effect in the physical activity of rodents (Teske and Mavanji, 2012). Concurrently, OX deficiency/neuronal loss has been linked to narcolepsy, a sleep disorder characterized by the sudden intrusion of sleep and/or cataplexy and sleep attacks (Nishino et al., 2000; Ohno and Sakurai, 2008; Sellayah and Sikder, 2013; Tsujino and Sakurai, 2013).

Few studies have examined relationships among plasma OXA concentrations, nutritional status, and sleep processes in AN. Bronsky et al. (2011) found baseline plasma OXA concentrations to be elevated in AN compared to those of HC, while Janas-Kozik et al. (2011) reported lower concentrations in their AN sample. Both studies showed plasma concentrations to decrease with re-feeding (Bronsky et al., 2011; Janas-Kozik et al., 2011). To our knowledge, no study to date has examined whether or not OXA is associated with the sleep disturbances in AN. In a related vein, the bearing of OXA concentrations upon outcome has not been previously studied.

The objectives of this study were to explore the relationship between OXA concentrations and sleep behavior in AN and normal weight controls (HC), and to examine how OXA concentrations and sleep may be related to treatment outcome. Based on the available literature, we anticipated that higher plasma OXA concentrations would be associated with poorer sleep quality in both AN and HC, although we expected sleep disturbances to be more pronounced in AN participants. Furthermore, we expected OXA concentrations to be associated with poorer sleep quality, and both to have a negative effect on treatment outcome.

2. Method

2.1. Participants

Participants in this study included 48 women with AN (BMI < 18.5 kg/m^2) and 98 female HC (BMI = 18.5–24.9 kg/m^2). The AN participants were diagnosed using DSM-IV-TR criteria (American Psychiatric Association, 2000) and were consecutively admitted female patients to the Day Hospital Treatment Program at the ED Unit of the University Hospital of Bellvitge (Barcelona, Spain). ED diagnoses were established via the face-to-face semi-structured clinical interview (SCID-I) (First et al., 1997). Mean age of all participants was 27.5 years (SD = 8.2). Clinical and control groups did not differ as to age (control mean = 27.5 ± 7.9, AN mean = 27.2 ± 8.7, $p = .84$). A total of 15 AN patients were taking antidepressants and 14 benzodiazepine—anxiolytics/hypnotics.

Participants were excluded if their age was below 18 or above 60 years. Males were excluded from the study given the low prevalence of male AN patients and inclusion of this group might confound results. To be eligible for the HC group, participants had to be free of any ED history and to have a BMI between 18.5 and 30 kg/m^2. The physical and mental health of the HC participants was evaluated by means of the General Health Questionnaire-28 (GHQ-28) (Goldberg, 1978). HC participants were recruited via word-of-mouth and advertisements posted around university and hospital areas (CIBERobn Spanish Research Network). All participants gave written informed consent to participate in this Institutional Research Ethics Committee approved study, conducted in accordance with the Declaration of Helsinki.

2.2. Treatment protocol

After an initial assessment, the AN patients received treatment-as-usual, consisting of a 12-week manualized Day Hospital Program as previously described (Fernández-Aranda and Turón Gil, 1998; Custal et al., 2014), throughout which the patients participated in group therapy sessions covering both nutritional and