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NREM SLEEP HYPERSOMNIA AND REDUCED SLEEP/WAKE CONTINUITY IN A NEUROENDOCRINE MOUSE MODEL OF ANXIETY/DEPRESSION BASED ON CHRONIC CORTICOSTERONE ADMINISTRATION

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Abstract—Sleep/wake disorders are frequently associated with anxiety and depression and to elevated levels of cortisol. Even though these alterations are increasingly sought in animal models, no study has investigated the specific effects of chronic corticosterone (CORT) administration on sleep. We characterized sleep/wake disorders in a neuroendocrine mouse model of anxiety/depression, based on chronic CORT administration in the drinking water (35 μg/ml for 4 weeks, ''CORT model''). The CORT model was markedly affected during the dark phase by non-rapid eye movement sleep (NREM) increase without consistent alteration of rapid eye movement (REM) sleep. Total sleep duration (SD) and sleep efficiency (SE) increased concomitantly during both the 24 h and the dark phase, due to the increase in the number of NREM sleep episodes without a change in their mean duration. Conversely, the total duration of wake decreased due to a decrease in the mean duration of wake episodes despite an increase in their number. These results reflect hypersomnia by intrusion of NREM sleep during the active period as well as a decrease in sleep/wake continuity. In addition, NREM sleep was lighter, with an increased electroencephalogram (EEG) theta activity. With regard to REM sleep, the number and the duration of episodes decreased, specifically during the first part of the light period. REM and NREM sleep changes correlated respectively with the anxiety and the anxiety/depressive-like phenotypes, supporting the notion that studying sleep could be of predictive value for altered emotional behavior. The chronic CORT model in mice that displays hallmark characteristics of anxiety and depression provides an insight into understanding the changes in overall sleep architecture that occur under pathological conditions.

Key words: sleep disorders, hypersomnia, sleep/wake continuity, corticosterone, anxiety/depression, behavior.

INTRODUCTION

Sleep disorders are one of the early clinical symptoms observed in mental diseases, including depression (Riemann et al., 2001). Subjects with altered sleep patterns are ten times more likely to develop depression than individuals without sleep complaints (Taylor et al., 2005). Conversely, 50–90% of depressed patients exhibit poor sleep quality (Armitage, 2007). Sleep disorders encountered in depressive conditions can include some types of insomnia (20–80%) or hypersomnia (10–40%) (Kaplan and Harvey, 2009). According to clinical studies, the main sleep disturbances associated with depression are difficulties to initiate sleep and to maintain it, with early morning awakenings. Moreover, sleep architecture is modified by an increase in rapid eye movement (REM) sleep propensity leading to reduced REM sleep latency, reduced non-rapid eye movement (NREM) sleep and sleep fragmentation. This leads to poor sleep quality and decreased continuity of sleep (Gronli et al., 2004).

Numerous studies have described sleep/wake disorders in stress-related animal models that recapitulate the physiopathology of anxiety/depression but none has focused on the specific effects of chronic corticosterone (CORT) administration on sleep. We recently developed a translational model, based on long-term oral CORT exposure (David et al., 2009), mimicking the hypothalamic–pituitary–adrenal (HPA) axis dysfunctions observed in depressed patients (Nemeroff, 1998; Holsboer, 2000). The CORT model is a chronic exposure method optimized for use in modeling the persistent anxiety/depression-like state in rodents. It allows

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Abbreviations: β-CD, β-cyclodextrin; CORT, corticosterone; CRH, corticotrophin-releasing hormone; EEG, electroencephalogram; EMG, electromyogram; EOG, electrooculogram; GR, glucocorticoid receptor; HPA, hypothalamo–pituitary–adrenal axis; MA(s), microarousal(s); MR, mineralocorticoid receptor; NREM sleep, non-rapid eye movement sleep; NSF, Novelty-suppressed feeding; OF, open field; REM sleep, rapid eye movement sleep; SCN, suprachiasmatic nucleus of the hypothalamus; SE, sleep efficiency (ratio of total sleep time/total recording time); SD, sleep duration; Veh, Vehicle.

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the assessment of multiple behavioral tests in the same animals using an etiologically relevant model of depression that is easily replicable between and within laboratories (David et al., 2009; David et al., 2010; Gould, 2011; Mendez-David et al., 2013). Chronic CORT administration induces high emotionality, associated with a decrease in neurogenesis (David et al., 2009) and altered pain sensitivity (Hache et al., 2012). Such behavioral and neurochemical alterations are reversed by classical and innovative antidepressants (Rainer et al., 2011; Hache et al., 2012). Interestingly, our group recently reported in this model a flattened circadian rhythm and decreased activity in the home-cage, especially during the dark phase (Rainer et al., 2011). Because such alterations might parallel sleep/wake modifications, we investigated, in this neuroendocrine mouse model with altered emotional behavior, the actual sleep/wake disorders in relation to the anxio/depressive-like phenotype.

EXPERIMENTAL PROCEDURES

Animals

Twenty-four to twenty six adult male C57BL/6J mice (Janvier Labs, Saint-Quentin Fallavier, France), 7–8 weeks old (20–25 g) at the beginning of the treatment, were used in experiments. Mice were group-housed (five per cage) and kept under standard conditions: 12-h light/dark cycle with lights on at 7:00 AM, 21 °C ± 1 °C, 60% relative humidity, food (standard A04 SAFE food pellet) and water available *ad libitum*, throughout the experimental period. After a 4-week treatment by corticosterone (CORT-mice) or β-cyclodextrin (β-CD) (vehicle-mice), mice underwent a surgical implantation of electrodes for sleep evaluation. Mice were isolated from the recovery surgical period (1 week) until the end of the experiment in order to prevent the animals gnawing at electrode connectors. Separated groups (n = 8–10) were used to assess novelty-suppressed feeding test to investigate if sleep modifications could be correlated with this composite behavioral test. Throughout the study, we have selected only animals for which we obtained perfect sleep recordings and used behavioral results obtained in the same animals to correlate both parameters (sleep and behavior). All testing was conducted in compliance with protocols approved by the Institutional Animal Care and Use Committee (Council directive 87-848, October 19, 1987, Ministère de l'Agriculture et de la Forêt, Service Vétérinaire de la Santé et de la Protection Animale; permission 92-256B to D.J.D.).

Drugs and reagents

The dose and duration of vehicle and CORT treatments were selected based on previous studies (David et al., 2009; Rainer et al., 2011). The vehicle solution (0.45% β-CD) was made by dissolving β-CD powder (Sigma–Aldrich, Saint-Quentin Fallavier, France) in water (20%) with magnetic agitation and then diluted until the appropriate concentration (0.45%). The CORT solution (35 μg/ml equivalent to about 5–7 mg/kg/d), was prepared by dissolving the CORT powder (Sigma–Aldrich, Saint-Quentin Fallavier, France) by a sonication step in 20% vehicle solution. CORT treated-mice received 35 μg/ml CORT dissolved in β-CD and control mice receive β-CD (0.45%) alone. All treatments (vehicle and CORT), were administered per os in drinking water available *ad libitum*, delivered in opaque black bottles and changed every 4 days.

Behavioral tests

Open field (OF) test. This behavioral test characterizes anxiety-like behavior (Prut and Belzung, 2003; Dulawa et al., 2004; David et al., 2009). Measured parameters are entries and time spent at the center (defined by 21 × 21 cm^2 virtual area and assimilated as an anxiety-like area), at the periphery, locomotor activity and ambulatory distance during 30 min. Infra-red wall sensors in plexiglas open field boxes 43 × 43 cm^2 (Med, Associates, Georgia, VT, USA) allowed to record measured parameters. An anxiety-like phenotype was associated with decreased values of number of entries and time spent in the center.

Fur coat state test (CT). This test evaluates the depression-like state of CORT-mice via their grooming capacity by assigning a fur coat state score (Griebel et al., 2002; Santarelli et al., 2003; Surget et al., 2008). The total score of animals was defined as the sum of scores from five body parts. An animal not prone to depression-like phenotype will have a normal grooming activity and a net coat condition with a low score, and conversely.

Novelty-suppressed feeding (NSF). NSF paradigm is a conflict test that elicits competing motivational situation between feeding desire and the aversion that can have animals to move and venture in a novel environment brightly lit at the center (anxiety-like area). As previously described (Santarelli et al., 2003; David et al., 2009), 24 h before the test, animals were put in fasted condition and home cages and grids were changed. NSF apparatus was a rectangular box (50 × 40 × 20 cm) filled with sawdust with a similar granule that those usually used and placed at the center of the box. Before the test, each animal was weighed to estimate the loss of weight due to the 24-h food deprivation. This test, carried out over 10 min (maximal period), measured the latency to feed in an aversive environment. After the test, animals were returned to their home cages to evaluate the food consumption of a pellet during 5 min. An anxiety/depressive-like phenotype was linked to increased latency to feed.

All behavioral tests were conducted and without the knowledge of the treatment arm of the mice studied.

Surgical procedure of implantation of electrodes for polygraphic sleep-wakefulness monitoring

All mice were implanted with electrodes for polygraphic sleep/wake monitoring (enamelled nichrome wire,