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INCREASES IN MATURE BRAIN-DERIVED NEUROTROPHIC FACTOR PROTEIN IN THE FRONTAL CORTEX AND BASAL FOREBRAIN DURING CHRONIC SLEEP RESTRICTION IN RATS: POSSIBLE ROLE IN INITIATING ALLOSTATIC ADAPTATION

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Abstract—Chronic sleep restriction (CSR) has various negative consequences on cognitive performance and health. Using a rat model of CSR that uses alternating cycles of 3 h of sleep deprivation (using slowly rotating activity wheels) and 1 h of sleep opportunity continuously for 4 days ('3/1' protocol), we previously observed not only homeostatic but also allostatic (adaptive) sleep responses to CSR. In particular, non-rapid eye movement sleep (NREMS) electroencephalogram (EEG) delta power, an index of sleep intensity, increased initially and then declined gradually during CSR, with no rebound during a 2-day recovery period. To study underlying mechanisms of these allostatic responses, we examined the levels of brain-derived neurotrophic factor (BDNF), which is known to regulate NREMS EEG delta activity, during the same CSR protocol. Mature BDNF protein levels were measured in the frontal cortex and basal forebrain, two brain regions involved in sleep and EEG regulation, and the hippocampus, using Western blot analysis. Adult male Wistar rats were housed in motorized activity wheels, and underwent the 3/1 CSR protocol for 27 h, for 99 h, or for 99 h followed by 24 h of recovery. Additional rats were housed in either locked wheels (locked wheel controls [LWCs]) or unlocked wheels that rats could rotate freely (wheel-running controls [WRCs]). BDNF levels did not differ between WRC and LWC groups. BDNF levels were increased, compared to the control levels, in all three brain regions after 27 h, and were increased less strongly after 99 h, of CSR. After 24 h of recovery, BDNF levels were at the control levels. This time course of BDNF levels parallels the previously reported changes in NREMS delta power during the same CSR protocol. Changes in BDNF protein levels in the cortex and basal forebrain may be part of the molecular mechanisms underlying allostatic sleep responses to CSR. **© 2014 IBRO. Published by Elsevier Ltd. All rights reserved.**

Key words: sleep deprivation, Western blot, basal forebrain, frontal cortex, hippocampus, allostasis.

INTRODUCTION

Chronic sleep restriction (CSR), i.e., not obtaining adequate sleep over days, weeks, to even years, has become common in modern societies due to various factors including work demands, social pressures, lifestyle choices, and certain medical conditions (Bonnet and Arand, 1995; Broman et al., 1996). CSR is associated with deficits in cognitive performance and changes in mood regulation (reviewed in Banks and Dinges, 2011; Jackson et al., 2013). CSR also has negative effects on metabolic, endocrine, and immune functions, and is a risk factor for diabetes, obesity, and cardiovascular disease (reviewed in Van Cauter et al., 2008; Killick et al., 2012).

To study the neurobehavioral consequences of CSR and underlying mechanisms, our laboratory has developed a rat model of CSR ('3/1' model) that takes into account the polyphasic sleep patterns of rodents, as well as circadian regulation of sleep. In this model, alternating periods of 3 h of sleep deprivation (SD; using slowly rotating activity wheels) and 1 h of sleep opportunity (no rotation) are continuously imposed over 4 days (Deurveilher et al., 2012). This protocol reduced total sleep time by ~60% from baseline levels, and initiated both homeostatic and allostatic (adaptive) sleep responses that were strongly modulated by time of day. Homeostatic responses included rebound increases in non-rapid eye movement sleep (NREMS) and rapid eye movement sleep (REMS), and in NREMS electroencephalogram (EEG) delta power, a well-established measure

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Abbreviations: BDNF, brain-derived neurotrophic factor; CSR, chronic sleep restriction; EEG, electroencephalogram; hrBDNF, human recombinant BDNF; LWC, locked wheel control; NREMS, non-rapid eye movement sleep; SD, sleep deprivation; SR, sleep restriction; TBS-T, Tris-buffered saline solution with Tween-20; WRC, wheel-running control.

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of sleep intensity (Borbely and Achermann, 1999), during intermittent sleep opportunities across the 4 days. Allostatic responses included a gradual decline in the rebound of NREMS delta power during sleep opportunities over the 4-day period, and muted rebounds in NREMS and REMS, and the absence of rebound in NREMS delta power, after the 4 days of sleep restriction (SR; Deurveilher et al., 2012). Similar allostatic sleep responses to CSR have been reported by others, also in rodents (Kim et al., 2007, 2012; Clasadonte et al., 2014; but see Leemburg et al., 2010).

The molecular mechanisms underlying the allostatic sleep responses to CSR are largely unknown. One molecule possibly involved in this process is brain-derived neurotrophic factor (BDNF), a member of the nerve growth factor family of neurotrophins with a critical role in neuronal survival and differentiation during development, and in synaptic plasticity in both developing and adult brains (reviewed in Lu, 2003; Park and Poo, 2013). Several lines of evidence implicate BDNF in the regulation of NREMS EEG delta power. Levels of BDNF mRNA in the cerebral cortex increased after 6 h of SD, and this increase was positively correlated with an increase in slow wave (or delta) activity during subsequent sleep in rats (Huber et al., 2007b). Furthermore, cortical BDNF injections increased slow wave activity during NREMS, while injections of a function-blocking BDNF antibody reduced it (Faraguna et al., 2008). In humans, the Val66Met polymorphism in the BDNF gene, which impairs activity-dependent BDNF protein secretion, was associated with reduced NREMS EEG delta power during both baseline and recovery following 40 h of SD (Bachmann et al., 2012). Thus, BDNF is an attractive molecule to study for understanding mechanisms involved in the allostatic EEG delta responses to CSR.

In the present study, we examined whether the 3/1 CSR protocol affects the brain levels of BDNF protein in rats, using Western blot analysis. We evaluated the changes in BDNF levels after either 27 or 99 h of CSR (Experiment 1), and after 24 h of unrestricted sleep following 99 h of CSR (Experiment 2). Wheel-running control (WRC) and locked wheel control (LWC) rats were allowed to sleep *ad libitum*. Levels of mature BDNF were measured in the frontal cortex and basal forebrain, two brain regions known to be involved in regulating sleep and EEG activity including slow waves (reviewed in Deurveilher and Semba, 2011; Riedner et al., 2011), and the hippocampus, an area that is not known to be directly involved in sleep regulation.

EXPERIMENTAL PROCEDURES

Animals

Adult male Wistar rats ($n = 42$; Charles River Canada, St. Constant, Quebec, Canada) were used; they weighed 296–412 g at the start of the CSR/control protocol. Upon arrival, animals were housed in pairs under a 12-h-light: 12-h-dark cycle (lights on at 07:00 AM) in a temperature-controlled (23 ± 1 °C) animal colony room, with *ad libitum* access to food and water, for a minimum of one week prior to the experiment. Animal-handling procedures followed the guidelines of the Canadian Council on Animal Care, and were approved by the Dalhousie University Committee on Laboratory Animals.

The 3/1 CSR protocol

The 3/1 CSR protocol was conducted by housing rats individually in programmable, motorized activity wheels (11 cm in width, 36 cm in diameter; model 80860, Lafayette Instrument, Lafayette, IN, USA), as previously described (Deurveilher et al., 2012). The wheels were placed inside individual experimental chambers which were each equipped with a fan and a light controlled by a timer to maintain the same 12-h-light: 12-h-dark cycle as in the animal colony room. Food and water were available *ad libitum*. Rats were subject to alternating periods of 3 h of SD imposed by slow rotation of the activity wheel (at ~2.5 m/min), and 1 h of sleep opportunity (no wheel rotation) continuously for either 27 h (Experiment 1) or 99 h (Experiments 1 and 2). Although all the wheels were programed to rotate at the same rate, we found that the actual number of rotations varied slightly among them, presumably due to variability in their mechanical performance (see the Results). When the wheels were rotating slowly during the SD periods, rats adjusted postures, walked slowly, or rode in the wheel for a few seconds. During these 'riding' intervals, rats could eat, drink, groom, or lie down.

Experimental design

Experiment 1. Rats were randomly divided into four treatment groups ($n = 6$/group): (1) SR2 group, which was sleep restricted for 27 h; (2) SR5 group, which was sleep restricted for 99 h; (3) WRC group; and (4) LWC group.

The SR2 and SR5 rats were housed in locked activity wheels for a 4 or 5-day habituation period prior to the 3/1 CSR protocol. During the habituation period, the activity wheels rotated for periods of 5–20 min (at ~2.5 m/min) once a day during the light phase, to allow the rats to become accustomed to the wheel rotations; the wheels were otherwise locked. The 3/1 CSR protocol began at lights on and continued for either 27 h (i.e., until the end of the first 3 h of SD in the light phase on day 2 of CSR [SR2]) or 99 h (i.e., until the end of the first 3 h of SD in the light phase on day 5 of CSR [SR5]).

The WRC rats were housed in wheels that were unlocked at all times, so rats could turn them freely, for a 9 or 10-day period to match the habituation and CSR periods in the SR5 group. The amount of activity in the WRC rats was monitored as the number of wheel rotations per h using AWM software (Lafayette). The LWC rats were housed in locked activity wheels and left undisturbed, also for a period of 9 or 10 days.

Experiment 2. In Experiment 1, we observed increases in BDNF protein levels in the SR2 and SR5 groups (see Results). To assess whether BDNF protein levels would return to control levels 24 h after 4 days of

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