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Brain Research

Research Report

Sleep allostasis in chronic sleep restriction: The role of the norepinephrine system

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ARTICLE INFO

Article history:
Accepted 27 July 2013
Available online 2 August 2013

Keywords:
Chronic sleep restriction
Allostasis
Norepinephrine
Rat

ABSTRACT

Sleep responses to chronic sleep restriction may be very different from those observed after acute total sleep deprivation. Specifically, when sleep restriction is repeated for several consecutive days, animals express attenuated compensatory increases in sleep time and intensity during daily sleep opportunities. The neurobiological mechanisms underlying these adaptive, or more specifically, allostatic, changes in sleep homeostasis are unknown. Several lines of evidence indicate that norepinephrine may play a key role in modulating arousal states and NREM EEG delta power, which is widely recognized as a marker for sleep intensity. Therefore, we investigated time course changes in brain adrenergic receptor mRNA levels in response to chronic sleep restriction using a rat model. Here, we observed that significantly altered mRNA levels of the α1- adrenergic receptor in the basal forebrain as well as α2- and β1-adrenergic receptor in the anterior cingulate cortex only on the first sleep restriction day. On the other hand, the frontal cortex α1-, α2-, and β1-adrenergic receptor mRNA levels were reduced throughout the period of sleep restriction. Combined with our earlier findings on EEG that sleep time and intensity significantly increased only on the first sleep restriction days, these results suggest that alterations in the brain norepinephrine system in the basal forebrain and cingulate cortex may mediate allostatic changes in sleep time and intensity observed during chronic sleep restriction.

1. Introduction

Sleep responses to chronic sleep restriction (CSR) may be very different from those observed after acute total sleep deprivation (SD). For example, short-term SD (i.e., 24 h or less) in animals as well as humans normally produces robust compensatory increases in sleep time and/or sleep intensity in the sleep episodes following the SD. However, when sleep time is reduced for several consecutive days, several studies have reported that rats adapt to the new sleep restriction (SR)

Abbreviations: AR, adrenergic receptor; BL, baseline; CSR, chronic sleep restriction; HSD, homeostatic sleep derive; LC, locus coeruleus; NE, norepinephrine; NREM, non-rapid eye movement; qRT-PCR, quantitative reverse transcription-polymerase chain reaction; R, recovery sleep; REM, rapid eye movement; SD, sleep deprivation; SO, sleep opportunity; SR, sleep restriction; WKY, Wistar-Kyoto; ZT, zeitgeber time

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http://dx.doi.org/10.1016/j.brainres.2013.07.048

condition by exhibiting attenuated (or non-significant) increases in sleep time or intensity during the daily sleep opportunities (Deurveilher et al., 2012; Kim et al., 2007, 2012; Lancel and Kerkhof, 1989; Rechtschaffen et al., 1999). Human CSR studies have also found adaptive sleep responses in that subjective sleepiness stabilizes at a mildly elevated level within the first 3 days of SR. However, objective sleepiness and neurobehavioral performance continue to worsen across SR days in humans and animals (Belenky et al., 2003; Carskadon and Dement, 1981; Kim et al., 2012; McCoy et al., 2013; Van Dongen et al., 2003). We recently reported that the brain adenosine system may mediate the continuous elevation in objective sleepiness observed during CSR in rats (Kim et al., 2012). However, it is still unknown what neurochemical mechanisms mediate the allostatic sleep responses, specifically the rapid adaptation of sleep time/intensity, observed during CSR.

Accumulating evidence suggests that locus coeruleus (LC) norepinephrine (NE) neurons may play a key role in regulating sleep duration and sleep intensity. For example, LC NE neurons in rodents stop firing before the transition from waking to sleep (Aston-Jones and Bloom, 1981) and before sleep-active neurons in the basal forebrain or preoptic hypothalamic neurons exhibit elevated discharge activities (Takahashi et al., 2010). These results suggest that sleep may be initiated by silencing wake-promoting neurons in the LC (Berridge, 2008; Takahashi et al., 2010). Even though electrical and pharmacological stimulation or inhibition of LC neurons alters arousal state, chemical or genetic ablation of LC NE neurons produces only small effects in sleep-wake amount, (Berridge, 2008; Blanco-Centurion et al., 2004; Gompf et al., 2010). This is likely due to compensation by other arousal promoting neuronal populations or within the NE system itself (Abercrombie and Zigmond, 1989; Harik et al., 1981), since maintaining wakefulness is critical for an animals' survival. However, selective lesion of LC NE neurons using the neurotoxin DSP-4 reduces NREM delta power in low frequency ranges (<1.5 Hz) during subsequent recovery sleep after 6 h SD (Cirelli et al., 2005), implying that NE tone during wakefulness affects NREM delta power during subsequent sleep. A recent optogenetic study also confirmed that LC NE neurons are actively involved in modulating sleep/wake time

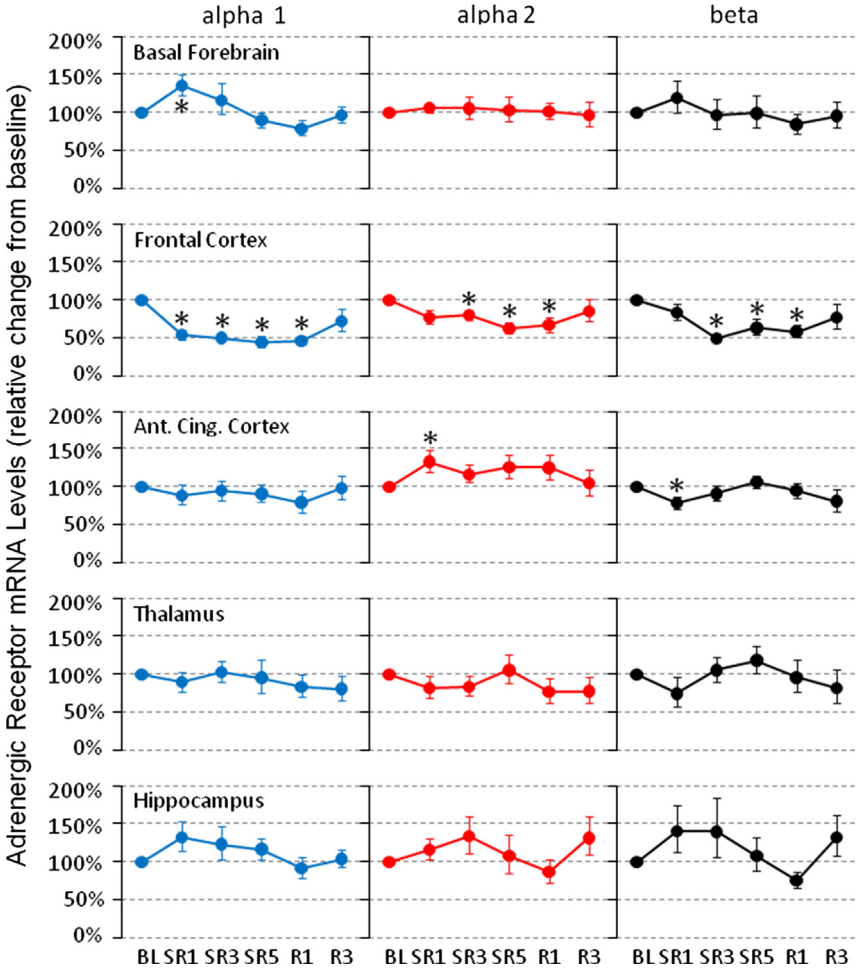

Fig. 1 – Adrenergic alpha 1, alpha 2 and beta receptor mRNA levels during chronic sleep restriction. **The brain tissue was collected at the light onset, which is immediately after 18 h sleep deprivation on sleep restriction (SR) days. The time course of changes (mean ± s.e.m.) show 2 major patterns: allostatic (basal forebrain alpha 1 and anterior cingulate cortex alpha 2 and beta) and homeostatic (all 3 receptor types in the frontal cortex). The asterisk (*) indicates statistical significance ($P<0.05$, $N=7–12$) compared to the BL.**