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NeuroImage

www.elsevier.com/locate/ynimg
NeuroImage 32 (2006) 1008–1015

A prominent role for amygdaloid complexes in the Variability in Heart Rate (VHR) during Rapid Eye Movement (REM) sleep relative to wakefulness

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Received 3 October 2005; revised 31 May 2006; accepted 1 June 2006
Available online 27 July 2006

Rapid eye movement sleep (REMS) is associated with intense neuronal activity, rapid eye movements, muscular atonia and dreaming. Another important feature in REMS is the instability in autonomic, especially in cardiovascular regulation. The neural mechanisms underpinning the variability in heart rate (VHR) during REMS are not known in detail, especially in humans. During wakefulness, the right insula has frequently been reported as involved in cardiovascular regulation but this might not be the case during REMS. We aimed at characterizing the neural correlates of VHR during REMS as compared to wakefulness and to slow wave sleep (SWS), the other main component of human sleep, in normal young adults, based on the statistical analysis of a set of $H_2{}^{15}O$ positron emission tomography (PET) sleep data acquired during SWS, REMS and wakefulness. The results showed that VHR correlated more tightly during REMS than during wakefulness with the rCBF in the right amygdaloid complex. Moreover, we assessed whether functional relationships between amygdala and any brain area changed depending the state of vigilance. Only the activity within in the insula was found to covary with the amygdala, significantly more tightly during wakefulness than during REMS in relation to the VHR. The functional connectivity between the amygdala and the insular cortex, two brain areas involved in cardiovascular regulation, differs significantly in REMS as compared to wakefulness. This suggests a functional reorganization of central cardiovascular regulation during REMS.

Keywords: REM sleep; Heart rate; Functional neuroimaging; Positron emission tomography; Functional connectivity; Amygdala; Insula

Introduction

Rapid eye movement sleep (REMS) is characterized by low-amplitude, relatively high-frequency electroencephalographic (EEG) rhythms, rapid eye movements and a complete muscular atonia interrupted by short muscular twitches. In addition, during REMS, neurovegetative regulation exhibits distinct features that are observed neither during wakefulness nor during non-REM sleep (NREMS). A striking example concerns thermoregulation. During REMS, a warm thermal load does not induce skin vasodilatation whereas a cold thermal load does not elicit any cutaneous vasoconstriction (Parmeggiani, 1980). These findings suggest that REMS is characterized by an "open-loop" mode of regulation, which does not rely on homeostatic feedback loops as strictly as during wakefulness or NREMS (Parmeggiani, 1985). During these 2 states, "closed-loop operations of automatic control mechanisms […] warrant an efficient and steady regulation of [autonomic] functions" (Parmeggiani, 1985). These rules presumably apply also to other neurovegetative systems. Accordingly, respiratory and heart rates are known to be much more variable during REMS than during NREMS or wakefulness (Orem and Keeling, 1980).

Although cardiovascular regulation is understood in detail, the cerebral correlates of VHR have been characterized only recently, and exclusively during wakefulness. In humans, VHR has primarily been related to the activity in the insular cortex. Intraoperative electrical stimulation of the insula elicits changes in heart rate and blood pressure (Oppenheimer et al., 1992). In normal subjects, functional neuroimaging studies showed that in response to physical exercise (Williamson et al., 1997, 1999) and mental stressor tasks (Critchley et al., 2000), both associated with significantly increased heart rate, the activity in both insula covaried with heart rate.

Heart rate regulation changes during sleep and has also been related to forebrain activity, as assessed by EEG recordings. For

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Available online on ScienceDirect (www.sciencedirect.com).

1053-8119/$ - see front matter © 2006 Elsevier Inc. All rights reserved.
doi:10.1016/j.neuroimage.2006.06.008

instance, EEG power spectral density relates to VHR indices (Otzenberger et al., 1997, 1998; Ehrhart et al., 2000; Brandenberger et al., 2001; Ako et al., 2003). However, the cerebral correlates of VHR during sleep needs to be further characterized, anatomically refined and described separately for NREMS and REMS. Indeed, heart rate regulation differs between these 2 types of sleep due to predominant parasympathetic and sympathetic drives, respectively (Brandenberger, 2005). In this paper, we were particularly interested in characterizing the cerebral correlates of VHR during REMS because of the intriguing autonomic control described in this stage of sleep. We hypothesized that during REMS, heart rate regulation involves the amygdala. This structure is one of the most active brain areas during REMS in man (Maquet et al., 1996). Due to its anatomical connectivity, it is in good position to influence key regions involved in cardiovascular regulation like the hypothalamus and the parabrachial complex in the brainstem (Hopkins and Holstege, 1978). The paraventricular nucleus of the hypothalamus is a key site for regulating autonomic activities such as blood pressure and heart rate (Coote, 1995; Xia and Krukoff, 2003). The parabrachial complex is known to be implied in the regulation of sympathetic activity and heart rate (Henderson et al., 2002).

We examined the cerebral correlates of VHR in REMS, as compared to wakefulness and SWS, in humans, using positron emission tomography (PET). To do so, we conducted a retrospective analysis on a set of PET scans acquired in 13 non-sleep deprived normal participants during SWS, REMS or wakefulness with simultaneous electroencephalographic and electrocardiographic recordings. We determined the brain areas where the regional blood flow (CBF) was more tightly related to the VHR during REMS than during wakefulness, during SWS than during wakefulness or during SWS than during REMS. We focused on a set of target areas identified as critical in autonomous regulation during wakefulness: the insula (Cechetto and Saper, 1987; Oppenheimer et al., 1992; Oppenheimer, 1994; Corfield et al., 1995; Oppenheimer et al., 1996; Williamson et al., 1997; Critchley et al., 2000), the amygdala (Orem and Keeling, 1980; Sei and Morita, 1996; Critchley et al., 2000), the hypothalamus (paraventricular nucleus) (Hopkins and Holstege, 1978; Coote, 1995; Xia and Krukoff, 2003) and the midbrain (Herbert et al., 1990; Chamberlin and Saper, 1992; Henderson et al., 2002). Other areas more occasionally implicated in heart rate regulation were also considered as potential regions of interest: the hippocampus (Rowe et al., 1999; Ribeiro et al., 2002; Pedemonte et al., 2003), the anterior cingulate cortex (Buchanan et al., 1985; Neafsey, 1990), the ventromedial prefrontal cortex (Buchanan et al., 1985; Neafsey, 1990), the motor cortex (Critchley et al., 2000), the neostriatum (Delgado, 1960; Bradley et al., 1987, 1991; Lin and Yang, 1994; Critchley et al., 2000), the cerebellum (Delgado, 1960; Bradley et al., 1987, 1991; Lin and Yang, 1994; Critchley et al., 2000) and the brainstem areas of the pons and medulla (Willette et al., 1984; Allen and Cechetto, 1992; Critchley et al., 2000).

Methods

Subjects and experimental protocol

Data were obtained from previous sleep studies conducted in our center using the $H_2{}^{15}O$ infusion method (Maquet et al., 2000; Peigneux et al., 2003). All subjects were young, healthy, right-handed and male volunteers ($n=13$; age range 20–30 years) who gave their informed consent to participate in studies approved by the Ethics Committee of the Faculty of Medicine of the University of Liège. All had normal sinus rhythm and regular sleep–wake habits. None had any medical, surgical or psychiatric history; none was taking medication. Each subject spent three consecutive nights in the PET scanner at usual sleep time. Polysomnography monitoring during the first two nights allowed us to check for any abnormality in sleep (insomnia, sleep fragmentation, REMS onset, etc.) and accustomed participants to the experimental setting. Participants were selected for the third night if they could maintain 20 min of continuous stage 2, stages 3–4 of NREMS and REMS on both habituation nights. During the third night, PET scans were performed both during various stages of sleep when polysomnography showed steady characteristic sleep patterns and during waking at rest with eyes closed in complete darkness. During waking scans, the subjects had to stay still, eyes closed.

At least two waking, two stage 2, two stages 3–4 and two REMS scans were obtained in all subjects. In the present manuscript, we used 97 PET scans (30 during W, 29 during SWS and 38 during REMS) from 13 subjects who all had high-quality electrocardiographic (EKG) recordings in all the 3 main states of vigilance (wakefulness, NREMS, REMS). The same subjects were used for the delta analysis published by Dang-Vu et al. (2005).

Sleep analysis

Polysomnography was performed with a Synamp (Neuroscan, NeuroSoft Inc.K, Sterling, Virginia) system at 500 Hz or 1000 Hz, with a band width of 0.15–100 Hz. EEG on (at least) C3–A2 and C4–A1 derivations were recorded. In all cases, vertical and horizontal electrooculograms, chin electromyographic derivation and chest electrocardiogram were recorded on bipolar montage. Sleep scoring followed standard international criteria (Rechtschaffen and Kales, 1968).

Heart rate analysis

The analysis was performed on the 90-s recordings obtained during each PET scan. The EKG was visually checked in order to discard any period containing movement, muscle or breathing artefact. A template of the QRS complex was generated by averaging the QRS complexes over the whole 90 s of recording. A coefficient of correlation was computed at each time point between the template and the actual recording using a sliding window. Correlation coefficient above 0.80 was shown to reliably identify the occurrence of a QRS complex. This threshold was used to detect R events. RR intervals, from these tagged events were then computed, generating a new time series covering the whole 90-s scanning period. The variability in heart rate (VHR) was simply estimated as the standard deviation of the duration of RR intervals, as it has been described as a valid measure of the VHR (Malik, 1996).

PET data acquisitions

PET data were acquired on a Siemens CTI 951 R 16/31 scanner in three-dimensional mode. The head of the subjects was stabilized by a thermoplastic face mask secured to the head holder (Truscan Imaging, Annapolis, Maryland), and a venous catheter was inserted in a left antebrachial vein. First, a 20-min transmission scan was acquired for attenuation correction using three rotating