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Original Article

Sympathetic and cardiovascular changes during sleep in narcolepsy with cataplexy patients

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ABSTRACT

Objective: Neural mechanisms underlying sleep-onset rapid eye movement (REM) periods (SOREMPs) in narcolepsy and the role of hypocretin in driving sympathetic changes during sleep are misunderstood. We aimed to characterize autonomic changes during sleep in narcolepsy with cataplexy (NC) patients to clarify the nature of SOREMP events and the effect of hypocretin deficiency on sympathetic activity during sleep.

Methods: We observed 13 hypocretin-deficient NC patients and five healthy controls who underwent nocturnal video-polysomnography (v-PSG) with blood pressure (BP) recording, heart rate (HR), skin sympathetic activity (SSA), and muscle sympathetic nerve activity (MSNA) from the peroneal nerve by microneurography.

Results: Compared to wake, control participants displayed a progressive significant decrease of BP and sympathetic activities during nonrapid eye movement (NREM) sleep and an increase of autonomic activity during REM sleep, as expected. NC patients showed: (1) a decrease of sympathetic activities during SOREMP comparable to NREM sleep stage 1 (N1) but in contrast to the increased activity typical of REM sleep; and (2) physiologic sympathetic change during the following sleep stages with a progressive decrease during NREM sleep stage 2 (N2) and NREM sleep stage 3 (N3) and a clear increase in REM sleep, though BP did not show the physiologic decrease during sleep (nondipper pattern).

Conclusions: SOREMPs in NC patients lack the sympathetic activation occurring during physiologic REM sleep, thus suggesting a dissociated REM sleep condition. In addition, our data indicated that hypocretin plays a limited role in the regulation of sympathetic changes during sleep.

1. Introduction

Narcolepsy with cataplexy (NC) is a chronic sleep disorder characterized by a tetrad of symptoms with largely unknown underlying mechanisms [1]. It has long been claimed that NC symptoms reflect a pathologic activation of brainstem mechanisms inducing a full-blown rapid eye movement (REM) sleep intrusion into active wake, which could be responsible for sleep-onset REM periods (SOREMPs) and other NC symptoms [2,3]. However, the discovery of hypocretin (orexin) neuronal loss in the posterior hypothalamus pinpointed the central role of hypocretin deficiency in NC [4,5], which clashes with the hypothesis of a brainstem dysfunction underlying NC. Accordingly, studies on genetically inherited NC in Dobermans have shown that the mechanism responsible for muscle atonia causing cataplexy is likely located in the hypothalamus and differs from those responsible for REM sleep [6]. Further, autonomic changes during cataplexy differ from those occurring during REM sleep in humans [7].

The SOREMP polysomnographic (PSG) features have been characterized [8,9], but a description of associated autonomic changes is still lacking, thereby precluding a definite conclusion on the nature of SOREMP that may result from a displacement of REM sleep. Further, the role of hypocretin in regulating sympathetic activity during wake has been widely explored [10]; however, it is not clearly documented how it influences sympathetic activity during sleep in humans. Therefore, the aims of our study were to characterize the pattern of sympathetic and cardiovascular changes during SOREMP and the following sleep stages in hypocretin deficient NC patients to help clarify the nature of SOREMPs and the effect of hypocretin deficiency on sympathetic activity during sleep.

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2. Materials and methods

We studied 15 patients with NC confirmed by clinical assessment, by PSG followed by multiple sleep latency test (MSLT), or by low or undetectable cerebrospinal hypocretin-1 levels [11]. Patients were selected for the microneurographic study based on the following criteria: (1) no needle phobia, (2) recordable MSNA in a supine position evaluated by a preliminary wake recording, (3) no major body movements or motor activation during sleep as evaluated by a previous PSG, and (4) drug-naive patients. Microneurographic recording during sleep was successful in 13 NC patients (ages, 34 ± 11 years; five men [Table 1]), whereas two patients were unable to fall asleep. A microneurographic recording was attempted in 15 age-matched healthy controls, but only five controls who were not deprived of sleep (35 ± 21 years; two men) were able to fall asleep and show sleep cycles on the recording. The high dropout rate was likely due to the complex and uncomfortable setting including microneurography and 14 additional parameters. The experimental procedures were approved by the Local Ethics Committee at Bologna University and all participants gave their written informed consent to be enrolled in the study.

2.1. Video-PSG with microneurography

Three to four weeks after a diagnostic PSG, selected participants underwent a second experimental nocturnal video-PSG (v-PSG), including microneurography. During v-PSG recording electrodes were placed according to the international system for the visual scoring of sleep stages, including electroencephalogram (four channels), bilateral electrooculogram, and submentalis and bilateral anterior muscles tibialis electromyogram [12]. Additionally, the following parameters also were recorded during v-PSG: respiratory movements using a thoracic gauge; arterial finger blood pressure (BP), continuously monitored by the volume-clamp method (Finapress BP monitor, Ohmeda 2300, USA) with the cuff around the middle phalanx of the third left finger on the left hand; skin blood flow (Skin Vasomotor Response [SVR]) by an infrared photoelectric transducer (model PPS, Grass Instruments: filter setting 0.5–100 Hz) from the right hand; changes in skin potential (Skin Sympathetic Response [SSR]) by Ag-AgCl surface electrodes (filter setting, 0.1–100 Hz) from the right hand; and multiunit postganglionic muscle sympathetic nerve activity (MSNA) recorded with a tungsten microelectrode with a tip diameter of a few microns inserted into the left peroneal nerve posterior to the fibular head.

A low-impedance reference electrode was inserted subcutaneously a few centimeters away. The nerve signal was amplified (×50,000), filtered (band pass 700–2000 Hz), and fed through a discriminator for further noise reduction and audio monitoring. An MSNA burst represented a mean voltage (integrated) display of the original nerve signal and was obtained by passing the original signal through a resistance–capacitance circuit (time constant, 0.1 s). A recording of MSNA was considered acceptable when it revealed spontaneous pulse-synchronous bursts of neural activity that fulfilled the previously described criteria for MSNA [13].

2.2. Data analysis

2.2.1. Sleep scoring

Sleep stages were visually scored following standard criteria [12] on 30-s epochs. Sleep stages were classified into non-REM (NREM) sleep stage 1 (N1), NREM sleep stage 2 (N2), NREM sleep stage 3 (N3), and REM sleep. Before turning off the lights, 5 min of relaxed wakefulness were recorded from the participants who were invited to stay awake. Afterward, the lights were turned off and participants were allowed to sleep. The following sleep variables were obtained from the overnight study: total sleep time (TST), defined as the total hours of PSG-defined sleep; sleep efficiency (SE, %) was TST divided by lights-off time; sleep latency (SL), defined as the interval between lights off and the first three consecutive epochs of stage N1 sleep or 1 epoch of stages N2, N3 or SOREMP; and the sleep fragmentation index, calculated as the ratio between any sleep stage shift (including awakenings) and the TST per hour [14]. A SOREMP was defined as PSG REM sleep findings (disappearance of muscle tone associated with low-voltage high-frequency electroencephalogram and REMs) occurring within 15 min from sleep onset.

2.2.2. Sympathetic activity

MSNA was expressed as burst incidence (bursts/100 heartbeats). Sympathetic activity going to skin is expressed by the correspondent effector sympathetic responses such as SVR and SSR [15,16]. To simplify data, sympathetic outflow to skin was reported as skin sympathetic activity (SSA) expressing the mean value of both spontaneous SVR and SSR [17]. This choice also was justified,

Table 1
Demographic and clinical data of examined patients and control participants.

Patients	Age (y)	Sex	Dis. dur. (y)	Hypoc. level pg/mL*	MSLT		PSG			
					mSL	SOREMPs (n)	SL	TST (min)	SE (%)	SFI (n/h)
DR	30	F	10	30.8	2′ 0″	3	3′ 30″	44	83	35.5
PA	57	F	16	0	2′ 48″	4	6′	44	82	21
LS	38	M	5	14.3	4′ 42″	2	2′	72.5	79	35
LM	50	F	8	18.4	2′ 36″	5	10′	45	65	63
RA§	24	M	5	0	1′ 42″	4	1′ 30″	141	88	36
MG	26	M	10	0	5′ 4″	3	1′	93	79	17
TS	32	F	6	23.6	0′ 54″	4	4′ 30″	46	53	82
PG	20	F	6	11.2	1′ 0″	5	5′	30	75	24
GV	33	M	18	57.3	13′ 42″	2	6′	77	66	19
ZE	19	F	4	1.3	3′ 30″	5	3′	69	85	24
RM	38	F	23	49.8	7′ 24″	1	7′ 30″	55.5	69	40
AE§	32	F	13	0	2′ 0″	3	6′ 30″	148.5	85	49
FM	45	M	10	17.5	3′ 3″	4	5′	33.5	50	120
Mean	34 ± 11		10 ± 6	14 ± 15	4 ± 1	4 ± 1	4 ± 1	69 ± 38	73 ± 12	44 ± 30
Controls	35 ± 21		–	–	–	–	7 ± 1	69 ± 40	80 ± 17	20 ± 11

Abbreviations: y, years; Dis. dur., disease duration; Hypoc., hypocretin 1; MSLT, mean sleep latency test; PSG, polysomnography; mSL, mean sleep latency; SOREMPs, sleep-onset rapid eye movement periods; SL, sleep latency; TST, total sleep time; min, minutes; SE, sleep efficiency; SFI, sleep fragmentation index; n/h, number per hour F, female; M, male.

* Normal value ⩽110 pg/mL.

§ Patients showing SOREMPs and rapid eye movement sleep phases during the recording.