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Research report

Waking and sleeping in the rat made obese through a high-fat hypercaloric diet

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HIGHLIGHTS

- Wake is fragmented in diet-induced obesity.
- Wake is depressed in diet-induced obesity.
- REM sleep is enhanced in diet-induced obesity.
- Wake depression in obesity may be a behavioral adaption to reduce foraging chances.

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ABSTRACT

Sleep restriction leads to metabolism dysregulation and to weight gain, which is apparently the consequence of an excessive caloric intake. On the other hand, obesity is associated with excessive daytime sleepiness in humans and promotes sleep in different rodent models of obesity. Since no consistent data on the wake–sleep (WS) pattern in diet-induced obesity rats are available, in the present study the effects on the WS cycle of the prolonged delivery of a high-fat hypercaloric (HC) diet leading to obesity were studied in Sprague-Dawley rats. The main findings are that animals kept under a HC diet for either four or eight weeks showed an overall decrease of time spent in wakefulness (Wake) and a clear Wake fragmentation when compared to animals kept under a normocaloric diet. The development of obesity was also accompanied with the occurrence of a larger daily amount of REM sleep (REMS). However, the capacity of HC animals to respond to a "Continuous darkness" exposure condition (obtained by extending the Dark period of the Light–Dark cycle to the following Light period) with an increase of Sequential REMS was dampened. The results of the present study indicate that if, on one hand, sleep curtailment promotes an excess of energy accumulation; on the other hand an over-exceeding energy accumulation depresses Wake. Thus, processes underlying energy homeostasis possibly interact with those underlying WS behavior, in order to optimize energy storage.

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1. Introduction

A possible link between insufficient sleep and metabolism dysregulation has been suggested by studies showing that a prolonged sleep curtailment may act as a key co-factor for the development of obesity and/or metabolic syndrome [1]. Sleep restriction protocols have been shown to reduce glucose tolerance and insulin sensitivity and to reduce the leptin/ghrelin ratio, possibly leading subjects to eat more than needed [1]. These data have been partly confirmed by the results of a recent study, showing that sleep restriction induced an increase in energy expenditure which was overcompensated by an increase in energy intake leading to weight gain, in spite of a concomitant increase in the leptin/ghrelin ratio [2].

However, it is worth noting that although the aforementioned effects appear to be very consistent on a short-term basis, the

Abbreviations: DD, continuous darkness; HC, hypercaloric; HCRT, hypocretinergic; Thy, hypothalamic temperature; LH, lateral hypothalamus; LD, light–dark; MA, motor activity; NREMS, non-REM sleep; nLab, normal laboratory conditions; NC, normocaloric; OP, obesity prone; OR, obesity resistant; POA, preoptic area; REMS, REM sleep; Wake, wakefulness; WS, wake–sleep.

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epidemiological evidence which is available so far does not appear strong enough to support the existence of a causal link between sleep curtailment and the development of obesity [3]. On the other hand, it has been shown in both humans [4] and mice [5,6] that obesity induced by an excess of food intake is *per se* associated with a decrease in the time spent in wakefulness (Wake) and an increase in the time spent in sleep. Similar changes to the wake–sleep pattern have also been observed in animals in which overfeeding was associated with a lack of either leptin peptide [7,8] or leptin receptors [9–11].

Both long-term sleep curtailment and overfeeding, leading to obesity, may functionally interact at a hypothalamic level, where circuits involved in WS and body metabolism regulation have been described [12,13]. Within the hypothalamic region, a possible site of interaction is the preoptic area (POA), which is crucially involved in the regulation of body temperature and, hence, of basal metabolism [14]. In particular, data from our laboratory have shown that a depression of cellular activity at the POA level is associated with a profound REMS dysregulation [15,16].

Since no consistent data on the wake–sleep (WS) pattern in diet-induced obesity rats are available, in the present study we have investigated the fine architecture of the WS cycle during the development of obesity induced by the administration of a high-fat hypercaloric (HC) diet in animals kept under a standard 12 h:12 h LD cycle.

The effects of the development of obesity on REMS regulation have been investigated in more detail by exposing the animals to 12 h of continuous darkness (DD), a condition obtained by extending the D period of the light–dark cycle to the following L period, which is known to enhance REMS occurrence in the albino rat [17] through an increase in the frequency of REMS episodes [15]. The practicality of this behavioral tool in the assessment of the intervention of POA circuits in shaping the interaction between weight gain and REMS occurrence has been suggested by the finding that REMS enhancement under DD is depressed when the cellular activity at POA level is impaired [15].

2. Materials and methods

2.1. Animals

Eighty adult male Sprague-Dawley rats (Charles River) were used. Animals were housed under normal laboratory conditions (nLab): free access to food and water, ambient temperature (Ta) 24.0 ± 0.5 °C, 12-h:12-h LD cycle (L: 09:00–21:00; 100 lux at cage level). The experiments were carried out according to the European Union Directive (86/609/EEC) and were under the supervision of the Central Veterinary Service of the University of Bologna and the National Health Authority.

2.2. Experimental protocol

After their arrival at the laboratory, all animals were fed a standard normocaloric (NC) laboratory diet (4RF21, Mucedola). Starting from the end of the sixth week of life, which was considered to be time = 0 of the experiment, animals were separated into two groups: the first group (n = 32) continued to be fed the standard NC diet, while the second group (n = 48) was fed a high-fat hypercaloric diet (PF4215, Mucedola: 35% fat). Both groups underwent EEG recordings after either 4 weeks (time = 4) or 8 weeks (time = 8) after diet differentiation. A group of animals was also studied at time 0. According to this protocol, five experimental groups were studied:

(i) Normocaloric diet at time = 0, NC0 (n = 8)
(ii) Normocaloric diet at time = 4, NC4 (n = 7)
(iii) High-fat hypercaloric diet at time = 4, HC4 (n = 7)
(iv) Normocaloric diet at time = 8, NC8 (n = 8)
(v) High-fat hypercaloric diet at time = 8, HC8 (n = 6)

Animals were selected randomly for the NC (NC0, NC4, NC8) and HC (HC4, HC8) diet protocols from each of 4 consecutive litters. The population of HC candidates was kept larger than its NC equivalent since about 50% of Sprague-Dawley rats fed a HC diet appear to be obesity resistant (OR) [18]. In order to study the WS pattern, animals assigned to each diet protocol had to undergo surgery by seven to ten days before the EEG recordings were carried out. Regarding the EEG recordings, the selection of the NC experimental groups was identical to that for the diet protocol, while that of the HC experimental groups was the result of a further random choice performed on animals whose weight was over the median value of the population (obesity prone, OP, animals).

For all groups, the EEG recordings were carried out under nLAB for two consecutive days (LD1, LD2). A third day of recording was added to both the NC8 and the HC8 groups, during which animals were kept under a DD condition. Under the DD protocol the environmental light was switched off during the normal 12-h L period of the LD cycle (DD-L) and kept off for the following 12-h D period (DD-D).

2.3. Surgery

While under deep general anesthesia (diazepam, Valium Roche, 5 mg/kg intramuscular; ketamine-HCl, Ketalar, Parke-Davis, 100 mg/kg intraperitoneal), 36 animals were implanted epidurally with two stainless-steel electrodes for frontal-parietal EEG recording. Furthermore, a thermistor mounted inside the tip of a stainless-steel needle (21G) was positioned above the left anterior hypothalamus to measure hypothalamic temperature (Thy). Plugs to connect EEG electrodes and the thermistor to the recording apparatus were embedded in acrylic dental resin (Res-Pal) anchored to the skull by small epidural stainless-steel screws implanted at the outer limit of the surgical field. Motor activity (MA) was monitored by means of a passive infrared detector (Siemens, PID11, Munich, FRG) placed on top of the recording cage.

2.4. EEG recordings

Animals were allowed to recover from surgery for at least one week, while adapting to the recording apparatus in individual Plexiglas cages kept in a thermoregulated and sound-attenuated box. After recovery from surgery, each rat was recorded continuously for 48 h, starting at the onset of the L period. The only exception was a brief time window from 09:00 to 09:15, during which bedding, food and water were changed.

Data were handled by software (QuickBASIC, Microsoft, CA, USA) developed in our laboratory. The EEG signal was amplified (amplification factor: approximately 7000), filtered (high-pass filter: −40 dB at 0.35 Hz; low-pass filter: −6 dB at 60.0 Hz) and, after analog-digital conversion (sampling rate: 128 Hz), was stored on a PC (486/100 DX-4). The EEG signal was subjected to online fast Fourier transform, and EEG power values were obtained for 4-s epochs in the Delta (DPW: 0.75–4.0 Hz), Theta (TPW: 5.5–9.0 Hz) and Sigma (SPW 11–16 Hz) bands. Thy signal was amplified (1 °C/1 V) before AD conversion (sampling rate: 8 Hz). MA signal was amplified and integrated before analog-digital conversion (sampling rate: 8 Hz) in order to make the output proportional to the amplitude and duration of movement (MA intensity). This system detected most of the movements related to the normal behavior of the rat, such as exploring, grooming, feeding and small movements during muscle twitching or brief awakenings in either non-REM sleep (NREMS) or REMS.

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