Sleep Enhances the Human Antibody Response to Hepatitis A Vaccination

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Objective: The common belief that sleep supports immune defense has received surprisingly little direct experimental support. The antibody response to vaccination provides a valid tool to assess the influence of sleep on adaptive immune functioning in humans, which is also clinically relevant. **Methods:** Two groups of healthy humans ($N = 19$) not previously infected with hepatitis A virus (HAV) were studied. On the night after primary vaccination with inactivated HAV, which took place at 0900 hours, one group had regular sleep. The other group stayed awake, and did not sleep before 2100 hours the following day. HAV antibody titers were measured repeatedly until 28 days after vaccination. Plasma hormone concentrations and white blood cell (WBC) subset counts were determined on the night and day after vaccination. **Results:** Subjects who had regular sleep after vaccination, displayed a nearly two-fold higher HAV antibody titer after 4 weeks than subjects staying awake on this night ($p=.018$). Compared with wakefulness, sleep after vaccination distinctly increased release of several immune-stimulating hormones including growth hormone, prolactin, and dopamine ($p < .01$). Concentrations of thyrotropin, norepinephrine, and epinephrine were lowered by sleep ($p < .02$), whereas sleep only marginally influenced WBC subset counts. **Conclusions:** Data suggest that sleep compared with sleep deprivation on the night after vaccination improves the formation of antigen-specific immune defense as reflected by antibody production in humans. Sleep presumably acts by inducing a hormonal environment in secondary lymphoid tissues, enhancing lymphocyte proliferation and differentiation and finally antibody synthesis. Results underscore the importance of sleep for immunocompetence. **Key words:** human, vaccination, memory.

HAV = hepatitis A virus; **WBC** = white blood cell; **TSH** = thyroid stimulating hormone.

INTRODUCTION

Sleep is often considered a state of the brain that improves immune function, although overall evidence for this notion is presently weak (1–3). Indirect evidence for this view derives from findings suggesting that sleep facilitates the extravasation of (certain types of) WBC, and increases the production of T-cell-derived cytokines such as interleukin-2 (IL-2), which are central for the development of an adaptive immune response (4, 5). However, those data do not directly prove a positive influence of sleep on host defense as launched by acute infection. The antibody response to vaccination represents a straightforward model for testing in vivo immune responses under experimental conditions in humans. Previous studies have indicated reduced antibody titers in response to hepatitis A vaccine and an influenza vaccine in subjects exposed to acute or chronic stressors (6, 7). However, effects of sleep on specific antibody formation after immunization so far have not been examined in humans. Also, only a few animal studies have addressed this issue using an influenza challenge (8–10). However, none of these studies focused on an examination of the *primary* response to antigen challenge, determining the generation of immunological long-term memories (11, 12). The present study aimed at showing in humans for the first time that in comparison with a night of sleep deprivation, regular nocturnal sleep after primary vaccination (with hepatitis A antigen) enhances antibody titers measured 4 weeks later.

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MATERIALS AND METHODS

Subject Characteristics

Twenty healthy volunteers (10 women) aged 20 to 35 years were recruited for the study after written informed consent was obtained. All subjects were nonsmokers and free of any medication during the whole study period. Acute and chronic illness as well as a previous infection with HAV were excluded by medical history, physical examination, and routine laboratory investigations, including WBC counts, determination of C-reactive protein, and an anti-HAV titer less than 10 mIU/ml. One subject was excluded because of increased liver enzymes and an inferred history of liver infection. Subjects were acclimatized to the experimental setting by an adaptation night (before the two experimental nights) that included the placement of electrodes for polysomnographic recordings and the insertion of an intravenous forearm catheter. The experimental protocol was approved by the local ethics committee.

Subjects had regular sleep–wake rhythms and had not been on night shifts for at least 4 weeks before the experiments. They reported going to bed usually between 2300 and 0100 hours and waking up between 0630 and 0830 hours. During the 6 days preceding the experiments, they were required to turn off lights for nocturnal sleep between 2300 and 2330 hours, to get up by 0700 hours the next morning, and not to take any naps during the day.

Procedure and Design

An experimental session started at 2100 hours and lasted 48 hours. Ten subjects (5 women) participated in the *sleep* condition, where subjects were examined during two consecutive regular 24-hour sleep–wake cycles with nocturnal sleep between 2300 and 0700 hours. The other nine subjects (four women) were assigned to the *wake* condition, during which they had a regular sleep-wake cycle within the first 24-hour period, but were kept awake during the second night. The wake period (after vaccination) covered an interval of 36 hours since subjects were not allowed to sleep until 2100 hours on the next day. During the nocturnal wake period, subjects stayed in bed between 2300 and 0700 hours (in a half-supine position) reading, watching television, and talking to the experimenter. The two experimental groups did not differ in age (25.42 ± 1.16 vs. 24.47 ± 1.24 years) or body mass index (23.81 ± 0.84 vs. 21.68 ± 0.76, for the sleep and wake group, respectively).

Vaccination took place at 0900 hours in the morning of the second day. Inactivated hepatitis A virus (1440 enzyme-linked immunosorbent assay [ELISA] units) adsorbed onto aluminum hydroxide (Havrix, SmithKline Beecham, Germany) were injected into the deltoid muscle of the nondominant arm. Subjects were blind to the experimental condition until 2100 hours of the second day, when participants of the sleep condition were prepared for standard polysomnography, while subjects of the wake condition were informed that they were to stay awake this night. For both experimental conditions, standardized meals including drinks were provided at appropriate times for breakfast, lunch, and dinner. During sleep deprivation, a light snack

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was offered around midnight. Caffeinated beverages were prohibited. Subjects were continuously observed by experimental staff, who recorded behavior and ensured that subjects did not fall asleep during wake periods. During daylight hours, subjects were allowed to walk around in the hospital area, but any kind of physically exhausting activity was prohibited. In fact, all subjects spent most of this time reading in a sitting position.

After insertion of an intravenous polyvinyl forearm-catheter, blood sampling started at 2100 hours (of the first night). Samples were subsequently drawn every 4 hours during nighttime and every 6 hours during daytime (2100, 0100, 0500, 0900, 1500, 2100 hours, etc). For blood sampling during sleep, the forearm catheter was connected to a long thin tube that allowed blood collection from an adjacent room without disturbing the subject's sleep. To prevent clotting, 300 ml of saline solution was infused throughout the night, regardless of whether subjects were kept awake or slept. During the daytime wake periods, body temperature (sublingually) and systolic and diastolic blood pressure were assessed at the same times that blood was sampled.

Dependent Measures, Assays, and Statistical Analysis

Antibodies against HAV were measured in serum by a commercial ELISA (Enzymun-Test Anti-HAV, Boehringer Mannheim) detecting IgM and IgG in total with a sensitivity less than 7 mIU/ml (13). Titers were measured daily in samples taken at 0900 hours on day 5 to 14 and again on day 28 after vaccination. Log transformed anti-HAV measures were used for analysis.

Based on standard sleep recordings, for each night sleep onset (with reference to lights off at 2300 hours), total sleep time, and percentage of total sleep time spent in the different sleep stages were determined (14). Latencies of sleep stage 2, slow wave sleep (SWS), and rapid eye movement (REM) sleep were assessed with reference to sleep onset.

Standard assays were used to determine concentrations of growth hormone (GH) (hGH-RIA, DPC, Bad Nauheim, Germany), prolactin (Aktiv-Prolaktin, DSL, Sinsheim, Germany), thyroid stimulating hormone (TSH) (TSH-LUMItest, Brahms Diagnostica, Berlin, Germany), and cortisol (Enzymun-test, Boehringer, Mannheim, Germany). Plasma levels of dopamine, norepinephrine, and epinephrine were determined by high-performance liquid chromatography. All measurements from an individual were performed in duplicate in the same assay. To determine WBC subset counts, blood samples were collected in EDTA tubes (Sarstedt, Nümbrecht, Germany) and stored at room temperature until assay. The total number of WBC, erythrocytes, and platelets, as well as leukocyte differential counts were determined automatically by a Technicon H1 counter (Technicon, Basingstoke, UK). Lymphocyte subsets were determined in whole blood by FACS analysis following standard methods (FACScan, Becton Dickinson, San Jose, CA). A minimum of 10,000 cells per sample were analyzed. To determine lymphocyte surface antigens, antibodies were conjugated with, respectively, fluorescein isothiocyanate (FITC) and phycoerythin (PE), and 20 μl of the conjugate was added to 100 μl EDTA blood. After a 15-minute incubation, erythrocytes were disintegrated and, after centrifugation, the supernatants were washed with phosphate-buffered saline. Enumeration by flow cytometry discriminated the following cells: T cells (CD3+; Leu-4/FITC), B cells (CD19+; Leu-12/PE), Th cells (CD4+; Leu-3a/FITC), cytotoxic T cells (CD8+; Leu-2a/PE), activated T cells (CD3+/HLA-DR; Leu-4/FITC/anti-HLA-DR+/PE), and NK cells (CD3−/CD16+; Leu-4/Leu-11c/FITC and CD56+; Leu-19/PE). All antibodies were purchased from Becton Dickinson (Heidelberg, Germany).

Statistical analysis of differences between the effects of the sleep versus wake condition relied on analysis of variance with a group factor (sleep/wake) and a repeated-measures factor (time) covering the different times of measurement after vaccination. Measures before vaccination were used as covariates. Degrees of freedom were corrected following the Greenhouse-Geisser procedure.

RESULTS

Both the group with regular sleep after vaccination as well as the group that was deprived of sleep on this night displayed low HAV antibody titers until about 8 days after vaccination (Fig. 1). Thereafter, anti-HAV titers increased to a greater

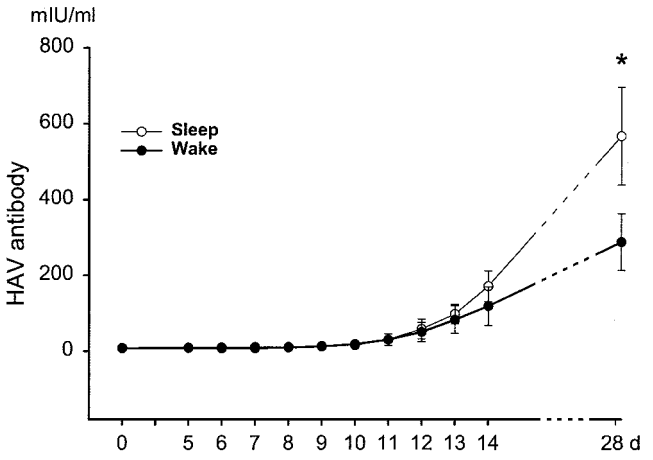

Fig. 1. HAV antibody titers. Mean (± SEM) anti-HAV titer in mIU/ml before (day 0) and after (days 5–14 and day 28) hepatitis A vaccination in subjects who had either regular sleep on the night after vaccination (thin line, open circles) or were kept awake on this night (thick line, filled circles). *p = .018, for comparison between the effects of sleep and the wakefulness on day 28.

extent in the sleep group as compared with the condition of sleep deprivation. On day 14 after vaccination, HAV antibody titers in the sleep group exceeded those of the sleep-deprived group on average by 44% (geometric mean ± SEM: 171.5 ± 39.9 vs. 119.0 ± 51.0 mIU/ml). On day 28, maximum antibody titers were revealed that were on average 97% higher in the subjects with regular nocturnal sleep than in the sleep-deprived subjects (567.6 ± 128.3 vs. 288.0 ± 75.3 mIU/ml; $F_{1,17} = 6.73$, $p = .018$, for pairwise comparison, $F_{10,170} = 4.10$, $p = .042$, for sleep/wake × time interaction).

Sleep on the night after vaccination in the sleep group was normal. Total sleep time amounted to 461.2 ± 5.5 minutes. The percentages of time spent in the different sleep stages were (mean ± SEM) 21.4 ± 2.4% for SWS, 20.0 ± 0.7% for REM sleep, 50.1 ± 2.3% for stage 2 sleep and 4.9 ± 0.7% for stage 1 sleep. Sleep architecture during this night did not differ significantly from that during the night before vaccination in this group, and also nights before vaccination did not differ between groups ($p > .3$ for all comparisons).

Compared with sleep deprivation, regular sleep after immunization was characterized by a distinct pattern of neuroendocrine changes (see Table 1 for a summary of endocrine and immune changes on the night and day after vaccination). Plasma concentrations of GH, prolactin, and dopamine were distinctly increased in the sleep condition as compared with continuous wakefulness. During early sleep, GH concentration was about four-fold higher than during the respective time in the wake condition (5.28 ± 1.3 vs. 1.34 ± 0.25 ng/ml, $p < .004$). The increasing effect of sleep on dopamine levels did not become evident until the succeeding daytime. Concentrations of TSH, norepinephrine, and epinephrine were lowered during sleep. A parallel decrease in cortisol concentration failed to reach significance ($p = .08$). TSH levels remained decreased also during the daytime after sleep. In addition, nocturnal sleep after vaccination was accompanied by a slight

TABLE 1. Endocrine and Immune Parameters During Nighttime and Daytime After Hepatitis A Vaccination for Sleep and Wake Conditions[a]

		Night			Day		
		Sleep	Wake	$p<$	Sleep	Wake	$p<$
		Mean SEM	Mean SEM		Mean SEM	Mean SEM	
GH	(ng/ml)	3.45 ± 0.81	1.51 ± 0.36	0.01	1.75 ± 0.18	1.56 ± 0.18	
Prolactin	(ng/ml)	17.01 ± 1.38	11.63 ± 1.46	0.005	12.16 ± 1.41	12.98 ± 1.49	
TSH	(mU/l)	1.32 ± 0.27	2.21 ± 0.25	0.005	1.13 ± 0.16	1.58 ± 0.16	0.02
Cortisol	(μg/dl)	4.80 ± 0.70	6.52 ± 0.87		11.4 ± 1.10	12.5 ± 1.20	
Dopamine	(ng/l)	15.4 ± 3.10	12.6 ± 3.90		24.5 ± 4.90	12.9 ± 3.60	0.01
Norepinephrine	(ng/l)	135 ± 13.0	173 ± 15.0	0.01	398 ± 50.0	362 ± 48.0	
Epinephrine	(ng/l)	14.5 ± 4.90	27.9 ± 10.2	0.02	41.1 ± 10.1	40.4 ± 9.20	
	in (1/nl)						
WBC		6.68 ± 0.63	7.30 ± 0.63		6.87 ± 0.50	6.59 ± 0.61	
Neutrophils		3.29 ± 0.10	4.18 ± 0.10	0.05	4.73 ± 0.46	4.10 ± 0.53	
Eosinophils		0.22 ± 0.03	0.16 ± 0.03		0.15 ± 0.03	0.12 ± 0.02	
Basophils		0.04 ± 0.01	0.03 ± 0.01		0.04 ± 0.01	0.03 ± 0.01	
Monocytes		0.42 ± 0.04	0.46 ± 0.04		0.40 ± 0.04	0.40 ± 0.04	
NK cells		0.12 ± 0.01	0.11 ± 0.01		0.20 ± 0.03	0.20 ± 0.03	
Lymphocytes		2.22 ± 0.15	2.30 ± 0.16		1.59 ± 0.13	1.81 ± 0.19	
T cells		1.80 ± 0.12	1.91 ± 0.15		1.21 ± 0.10	1.44 ± 0.18	
CD4+ T cells		1.06 ± 0.10	1.19 ± 0.11		0.71 ± 0.07	0.84 ± 0.07	
CD8+ T cells		0.77 ± 0.04	0.74 ± 0.10		0.60 ± 0.06	0.67 ± 0.15	
Activated T cells		0.13 ± 0.02	0.16 ± 0.04		0.10 ± 0.02	0.16 ± 0.06	0.03
B cells		0.33 ± 0.03	0.27 ± 0.03		0.20 ± 0.02	0.17 ± 0.02	

[a] "Night" values collapsed across samples collected at 0100 and 0500 h on the night after vaccination; "Day" values collapsed across samples at 0900 and 1500 h, the following day. Means are adjusted to prevaccination baseline values as derived from analysis of covariance. Significance ($p < .05$) for the difference between sleep and wake condition is indicated.

reduction in total WBC counts, reflecting primarily a diminished number of circulating neutrophils. Also, sleep decreased numbers of activated T cells, mainly during the daytime after the experimental sleep interval. Heart rate, blood pressure, and body temperature (measured during daytime) did not differ between conditions.

DISCUSSION

This study shows an enhanced formation of specific antibodies to hepatitis A antigen in humans who had regular sleep on the night after vaccination in comparison to a night of sleep deprivation. Although HAV antibody titers were on average distinctly higher already 14 days after vaccination in the group with regular *sleep* than in the *wake* group, the effect of sleep was greatest and most consistent on day 28. A 4-week interval is commonly used to evaluate clinical efficacy of hepatitis A vaccination because antibody formation is known to peak at this time (15). The manifestation of the effect at such a late phase suggests that sleep is involved in some fundamental processes of specific antibody formation. So far, effects of sleep on specific antibody formation after primary immunization have not been thoroughly examined in humans. Animal studies on this issue remained ambiguous. Brown et al. (8) observed in vaccinated mice a decreased antibody titer and virus clearance to a secondary influenza challenge, when this was followed by sleep deprivation. However, two further trials attempting to demonstrate similar effects of sleep deprivation on secondary antibody responses to influenza infection in mice failed (9, 10). Although these discrepancies highlight the complexity of sleep/immune interactions in which factors such as timing of sleep, the route of vaccine administration, and inherent features of the antigen may eventually determine the response amplitude, it should be noted that all those previous animal studies focused on influences of sleep on aspects of the secondary immune response. In contrast, the present data in humans revealing a sleep-induced increase in anti-HAV titers provide first evidence that sleep supports the emergence of a primary adaptive immune response. Sleep might in particular ease the induction of immunological memories, rather than the recall of maintained memories (3, 11, 16).

Mounting of a specific antibody response is a multistep, cascade-like process. At an initial stage, cells processing and presenting the antigen like macrophages/monocytes, dendritic cells, and neutrophils interact with T and B cells in a specific environment of cytokines to stimulate lymphocytic differentiation and eventually antibody secretion by plasma cells (17, 18). These processes take place to a great extent in secondary lymphoid tissues and are relatively slow, taking several days. Because the wake period in the sleep deprivation condition only covered the first 36 hours after vaccination, it presumably influenced the development of the specific antibody response at a rather early stage. Indicators reflecting these early steps of antibody response were not measured here. Notably, however,

previous experiments in humans not challenged by vaccination showed that sleep as compared with sleep deprivation enhances the T-cell production of IL-2, a most powerful activator of T- and B-cell differentiation (5). Also, the reduced counts for WBC subsets in circulating blood observed during sleep in other studies (4, 5) as well as here (for neutrophils and activated T cells expressing human leukocyte antigen–DR) could point to an increased extravasation of these cells that may eventually support acute immune processes in the tissue (19). That sleep affects the specific host defense via an influence on cell migration has been recently proposed based on animal data (9).

However, the effects of sleep on circulating immune cells after vaccination were mild in comparison with the profound sleep-induced alterations of endocrine activity. These included an increased release of GH, prolactin, and dopamine, and a diminished release of TSH, norepinephrine, and epinephrine. Although blood sampling frequency was kept low because of the long study period of 48 hours, which weakens reliability of the measurements, the major effects of sleep deprivation versus sleep on hormonal secretion shown in previous studies appeared to be reproduced. Although the hormonal regulation of specific immune defense is extremely complex (20, 21), it is likely that some of these endocrine changes contributed relevantly to the mechanisms mediating the immediate effects of sleep on anti-HAV titers. Although they are not obligate immunoregulators, both GH and prolactin have been proven to exert profound stimulating influences on various aspects of adaptive immune processes including the in vivo production of antibodies (21–25). Both GH and prolactin also share distinct augmenting effects on specific T-cell function, especially on the T-helper subsets (23, 25, 26). Additive facilitating influences on cell trafficking and viral defense might originate from the increase in dopamine concentration developing *after* regular sleep (27, 28). The relevance of the sleep-induced decreases in the concentration of TSH, norepinephrine, and epinephrine is less clear. Depending on the dose and experimental model used, for all of these hormones increasing as well as suppressing influences on aspects of adaptive immunity and antibody formation have been reported, and extrapolations to the conditions in healthy humans are presently not justified (29–31).

The pattern of hormonal changes argues against the view that acute stress during the wake condition reduced antibody formation. Foregoing studies in humans indicated that acute as well as chronic stressors can reduce the antibody titer response to hepatitis A vaccine or an influenza vaccine, and this was ascribed to increased release of glucocorticoids and catecholamines (6, 7). However, in the present study, the increase in cortisol concentration during the nocturnal vigil was negligible and remained nonsignificant. Concentrations of norepinephrine and epinephrine, although enhanced during nighttime wakefulness, were still distinctly lower than during daytime wakefulness (Table 1), and were by far lower than those typically associated with an acute stress response during the wake phase. Moreover, except for increased tiredness, assessment of self-reported mood (in the morning after experimental nights) did not provide evidence of increased feelings of strain in the wake condition, making a significant contribution of stress unlikely.

Overall, our data show that sleep orchestrates a coordinate pattern of neuroendocrine changes that could provide the decisive signal enhancing adaptive immune processes in secondary lymphoid tissue. Which of the humoral factors is most critical and whether sleep at a later stage of an emerging immune response acts differently, remain to be examined. The present data of reduced antibody formation after sleep deprivation also point to a link between poor sleep and clinically relevant decreases in immunoresponsiveness to vaccines (32). Results suggest that sleep should be considered an essential factor contributing to the success of vaccination.

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