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White blood cells and cortisol after sleep deprivation and recovery sleep in humans

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Abstract Sleep deprivation (SD) has enriched our treatment programme for major depression. SD has been demonstrated to modify different host defence activities. There is some evidence that there are reciprocal relationships between immune function and increased hypothalamic-pituitary-adrenocortical (HPA) axis activity in depression. We therefore investigated the number of leukocytes, granulocytes, monocytes, lymphocytes, B cells, T cells, helper T cells, cytotoxic T cells, NK cells and salivary cortisol in 10 healthy men before and after total SD (TSD) as well as after recovery sleep. Blood samples were drawn on 3 consecutive days at 7 am, 1 pm and 7 pm, respectively. Comparison of the 7 am values by contrast analysis yielded significant differences for granulocytes ($p = 0.044$) and NK cells ($p = 0.001$) after SD and recovery sleep. NK cells decreased and granulocytes increased after SD and after recovery sleep. Significant differences between single points in time across the day were found for granulocytes ($p = 0.022$), monocytes ($p = 0.031$), T cells ($p = 0.005$), helper T cells ($p = 0.004$), cytotoxic T cells ($p = 0.005$) and NK cells ($p = 0.017$). No significant difference could be detected for leukocytes, lymphocytes and B cells counts. These results favour the thesis that SD and recovery sleep lead to changes in the distribution of peripheral leukocytes, especially in a reduction of NK cells after SD and recovery sleep. The cortisol rhythm was affected neither by SD nor recovery sleep.

Key words Leukocyte · Subpopulation · Cortisol · Sleep deprivation · Depression

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Introduction

Sleep deprivation (SD) represents an effective treatment of depression with an overall response rate of about 50–60%. In contrast to pharmacological treatment regimes, the therapeutic effect develops rapidly, but a relapse into depression occurs in nearly 80 % of drug-free SD responders following consecutive daytime naps or nocturnal sleep (Wiegand et al. 1993; Wu & Bunney 1990).

Recent findings suggest changes in the host defence system in depression or during sleep and sleep deprivation, respectively. Sleep disorders are the most common symptoms in depression (Keup 1986). Stein et al. (1985) found a decrease in T and B cell number as well as in activity in depressed patients. Other hints for an altered host defence response in major depression are leukocytosis, monocytosis, neutrophilia, and elevation in platelet number (Seidel et al. 1996a), an increase of polyclonal B cells and of activated T cells, of the T helper/T suppressor cell ratio and of acute phase proteins, and a significantly higher production of different cytokines such as interleukin-1β (IL-1β) and interleukin-6 (IL-6) in culture supernatants of mitogen-stimulated peripheral blood mononuclear cells. Patients with bipolar depression show higher plasma levels for IL-1β, IL-6, interferon gamma, IL-1 receptor antagonist and soluble IL-2 receptors (sIL-2r). This production of IL-1β and sIL-2r is suppressed with the synthetic glucocorticoid dexamethasone in healthy controls compared to depressed patients (for review see Maes 1995 and Maes et al. 1991, 1992, 1993a, b, 1997). Depressive symptoms correlate negatively with the activ-

ity of natural killer (NK) cells (Irwin et al. 1990) and NK cell activity is raised when depressive symptoms reduced under pharmacotherapy (Irwin et al. 1992a). Dysthymia and depression is associated with elevated levels of NK cells (Ravindran et al. 1996; Seidel et al. 1996). Young adults with major depression have more circulating leukocytes and granulocytes, fewer NK cells, and less NK cell activity (Schleifer et al. 1996).

Many studies indicate that host defence mechanisms are also involved in the regulation of sleep (Krueger & Karnovsky 1987). In animal trials, the somnogenic potency of IL-1β was correlated with the injected dosage of IL-1β (Opp et al. 1992). An increase of non-rapid eye movement (NREM) sleep has repeatedly been reported after IL-1β. Correspondingly, the highest peaks for IL-1β were measured at the beginning of NREM sleep. This change in sleep profile resembles that of recovery sleep after SD. In line with these findings, an increase in plasma IL-1β is seen after SD (Krueger & Majde 1995) as well as a decrease of IL-1β during and after recovery sleep (Moldofsky et al. 1989; Dinges et al. 1995). Dinges et al. (1994) found leukocytosis and a decrease in helper T cell number in contrast to unaltered other lymphocyte subpopulations after SD. Partial SD (PSD) and total SD (TSD) led to a reduction of cell number and of activity of NK cells. After a night of recovery sleep, NK activity returned to baseline levels (Moldofsky et al. 1998; Irwin et al. 1996). A negative correlation is found between sleep disturbances and NK cell activity in depression (Cover & Irwin 1994). After stress and SD neutrophils and monocytes are increased; eosinophils and all lymphocytes subgroups are decreased (Boyum et al. 1996).

There is some evidence that there are reciprocal relationships between immune function and increased hypothalamic-pituitary-adrenocortical (HPA) axis activity in depression (Maes et al. 1996). In these patients the reduced response to the dexamethasone-suppression-test (DST) is a good characteristic (WHO study 1987). Mean 24-h cortisol and mean ACTH were increased in depressed male patients. The flattened circadian cortisol variation and reduced time of quiescence of cortisol secretory activity in patients suggest disturbances of circadian functions (Deuschle et al. 1997). In a study of Silberman and Post (1982) depressives showed besides a decreased REM latency an increased urinary-free cortisol. High cortisol/Dehydroepiandrosterone (DHEA) ratios at 8 pm and 12 pm predict persistent major depression in adolescence (Goodyer et al. 1998). DHEA levels are reduced in major depressive disorders in both adolescents and adults (Herbert 1998). The mean adrenal volume in depressives is 38 % larger (Rubin et al. 1996).

A temporal link between SWS and low cortisol release has been demonstrated (Gronfier et al. 1997). Free cortisol levels have increased by 50-70 % within the first 30 minutes after awakening (Preussner et al. 1997) and higher cortisol levels could be demonstrated in the evening following the night of SD (Leproult et al. 1997a). Staying awake during usual bedtime hours was associated with an acceleration in the rate of increase in sleepiness, which coincided with rapidly rising cortisol concentrations and maximal levels of melatonin in probands (Leproult et al. 1997b).

The elevated glucocorticoid secretion is made responsible for stress and/or depression induced suppression of host defence functions. Nevertheless most of the studies could not show a correlation between the cortisol concentration and the host defence functions after stress exposition or in depression (Irwin & Hauger 1988; Irwin et al. 1989; Keller et al. 1988; Miller et al. 1991).

Given the above mentioned interaction between depression and sleep with the host defence system and glucocorticoids, respectively, the aim of the present study was to investigate possible interrelationships between a well-established therapy for depression, SD, and the host defence system and cortisol. The hypothesis is that the biological parameters after SD correlate negatively with those in depression. The main emphasis was put on a detailed study of leukocyte subpopulations.

Subjects and methods

Experimental Design

Ten paid male volunteers (age: 27.4 ± 2.8 years) gave written informed consent before their participation in this investigation after the nature of the procedures had been fully explained to them. The medical history was carefully screened, and a thorough physical and psychiatric examination (including respective laboratory investigations) was carried out to exclude any actual or chronic illness (including sleep disorders) as well as stressful life events present.

The investigation took place on three consecutive days including a night of total sleep deprivation (TSD) between day 1 and day 2 and a recovery night between day 2 and day 3. During daytime, all participants followed their usual daily schedule. Whereas the night before and the night after TSD were spent at home to assure undisturbed nocturnal sleep (from 10 pm to 6 am (controlled by an alarm call service), TSD was carried out in our laboratory in groups of three or four participants, respectively. To prevent unwanted sleep including short naps, continuous supervision was provided. Blood samples were drawn on each day at 7 am, 1 pm and 7 pm after a rest period of at least 30 min, while the participants remained in half-supine position. Three days prior to as well as during the whole investigation the intake of pineapples, bananas, almonds, nuts, tomatoes, vanilla or alcohol was forbidden. All participants were non-smokers.

The experimental protocol was approved by the local ethics committee and has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

Differentiation of leukocytes

100 µl of blood and 10 µl of the specific Antibody Solution (FACS Ak, IQ Products, the Netherlands) were incubated for 30 min at room temperature in darkness.

- Differentiation of monocytes from leukocytes: Anti-CD 45 antibodies (leukocytes) and anti-CD 14 antibodies (monocytes) were incubated together.
- Differentiation of helper T cells from T cells: Anti-CD 3 antibodies (T cells) and anti-CD 4 antibodies (helper T cells) were incubated together.
- Differentiation of cytotoxic T cells from T cells: Anti-CD 3 antibodies and anti-CD 8 antibodies (cytotoxic T cells) were incubated together.

Table 1 Analysis of variance (ANOVA) with repeated measurements (day, time and interaction) and contrast analysis for the respective 7 am values

	Day		Hour		Interaction		Contrast	
	F(2,18)	p	F(2,18)	p	F(4,36)	p	F(2,18)	p
Granulocytes	1.02	0.39	5.70	0.022	0.6	0.65	4.33	0.044
Monocytes	5.12	0.017	4.22	0.031	0.88	0.48	1.40	0.27
T cells	0.02	0.98	6.70	0.005	0.56	0.69	0.78	0.47
Helper T cells	0.95	0.404	7.22	0.004	2.31	0.07	0.98	0.39
Cytotoxic T cells	2.02	0.16	7.27	0.005	0.11	0.98	1.25	0.31
NK cells	15.66	0.0001	5.14	0.017	0.65	0.62	18.14	0.001

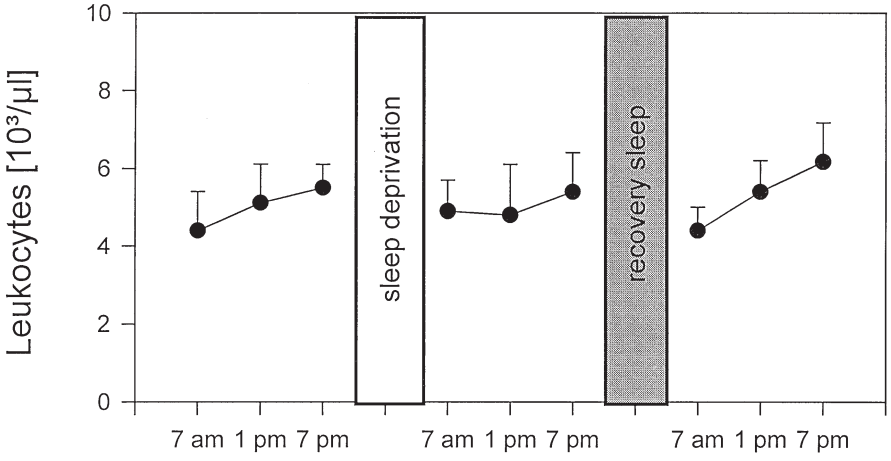

Fig. 1 Mean values (± standard deviations) of leukocytes before and after sleep deprivation as well as after recovery sleep

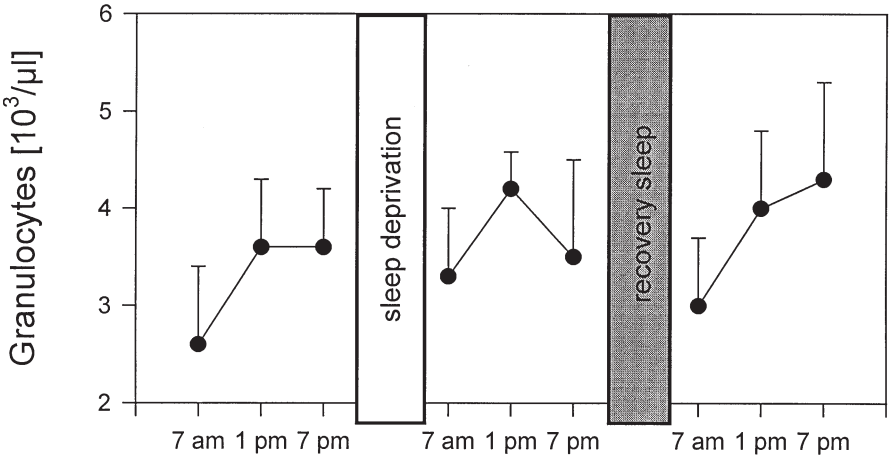

Fig. 2 Mean values (± standard deviations) of granulocytes before and after sleep deprivation as well as after recovery sleep

- Differentiation of B cells from lymphocytes: Anti-CD 3 Fits antibodies (lymphocytes) and anti-CD 19 Pe antibodies (B cells) were incubated together. Indirectly the number of T cells was determined.
- Differentiation of NK cells from T cells: Anti-CD 3 antibodies and anti-CD 16 antibodies (NK cell macrophages) as well as anti-CD 56 antibodies (NK cells) were incubated together.

Then the solutions were incubated with 2 ml lysis reagent for 10 min. After this step the solutions were centrifuged for 5 min at 4 °C at 300 g_{MAX}. The supernatant was discarded and the pellet was resuspendated with 2 ml PBS (2 % FCS) and again centrifuged in the above mentioned manner. The pellet was mixed with 500 µl sheet fluid. The result was obtained with FACS (Becton Dickinson FACS Scan, New Jersey).

- Granulocytes were counted in a cell counter.

Measurement of salivary cortisol

Saliva was obtained by using the Sarstedt Salivette (Sarstedt, Rommelsbach, FRG). This device contains a cotton wool swab which has to be inserted into the mouth for 5 minutes. After sampling saliva teh swab is removed into the Salivette and centrifuged at 1000 g_{MAX} for 10 min at 15 °C. At the bottom of the container 1-2 ml salvia was obtained. Afterwards the saliva sample was stored at –20 °C until assayed. All samples were analysed blind to the condition and in one assay to avoid variance due to inter-assay variance. Cortisol was determined by an adapted radioimmunoassay as described by Kirschbaum et al. (1989).

Data Analysis

For statistical evaluation, analysis of variance (ANOVA) with repeated measurements (two levels: day and hour) were used. A comparison by planned contrast analysis was performed to locate

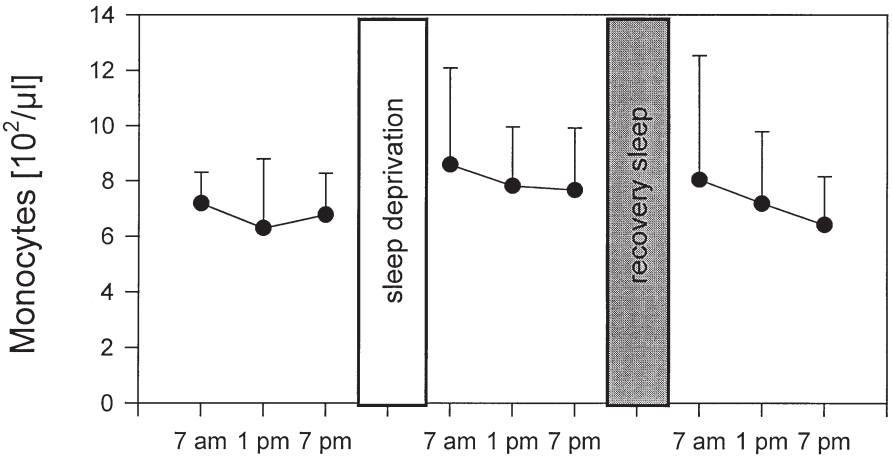

Fig. 3 Mean values (± standard deviations) of monocytes before and after sleep deprivation as well as after recovery sleep

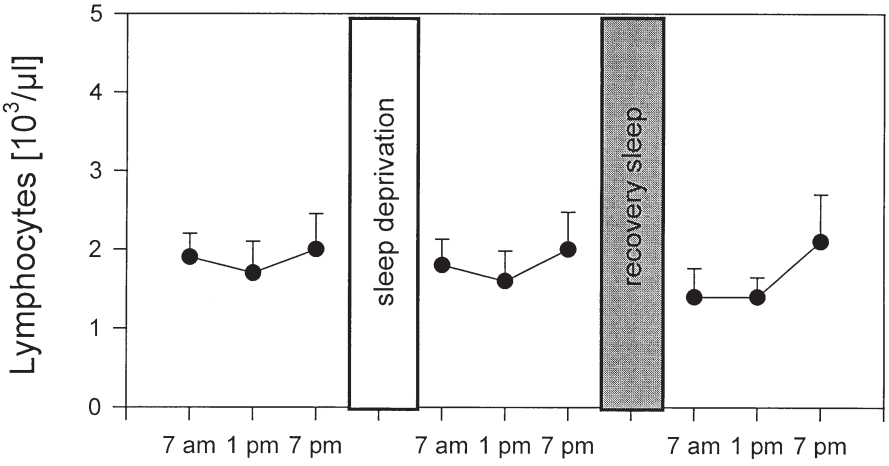

Fig. 4 Mean values (± standard deviations) of lymphocytes before and after sleep deprivation as well as after recovery sleep

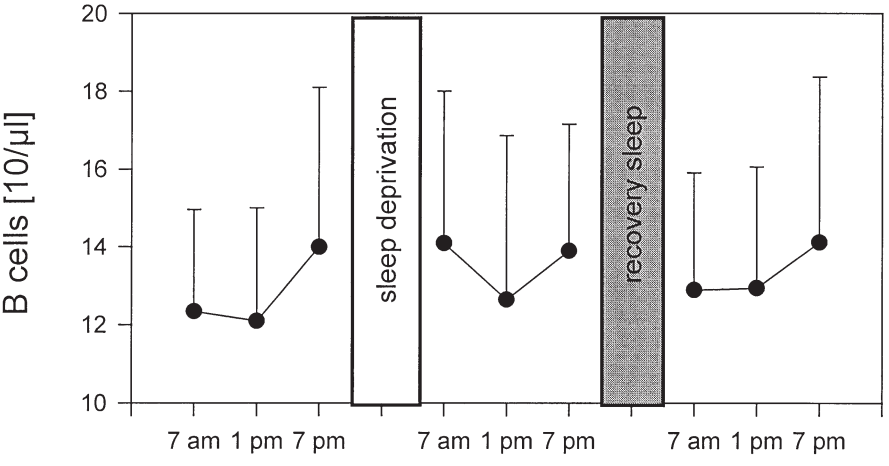

Fig. 5 Mean values (± standard deviations) of B cells before and after sleep deprivation as well as after recovery sleep

significant differences in the morning (7 am) between day 1, day 2 and day 3. The same ANOVA was performed for cortisol for the 7 am, 1 pm and 7 pm values The statistics were carried out using STATISTICA software (StatSoft Inc., Tulsa OK 74104, USA).

Results

The mean values (± standard deviations) of all parameters under investigation before and after TSD as well as after recovery sleep are shown in Figs. 1 to 10. ANOVA with repeated measurements revealed no significant differences concerning the overall time course pattern of granulocytes, monocytes, T cells, helper T cells, cytotoxic T cells and NK cells. Comparison of the 7 am values by contrast analysis yielded significant differences for granulocytes ($p = 0.044$) and NK cells ($p = 0.001$). NK cells decreased and granulocytes increased after SD and after recovery sleep. Significant differences between single points in time across the day were found for granulocytes

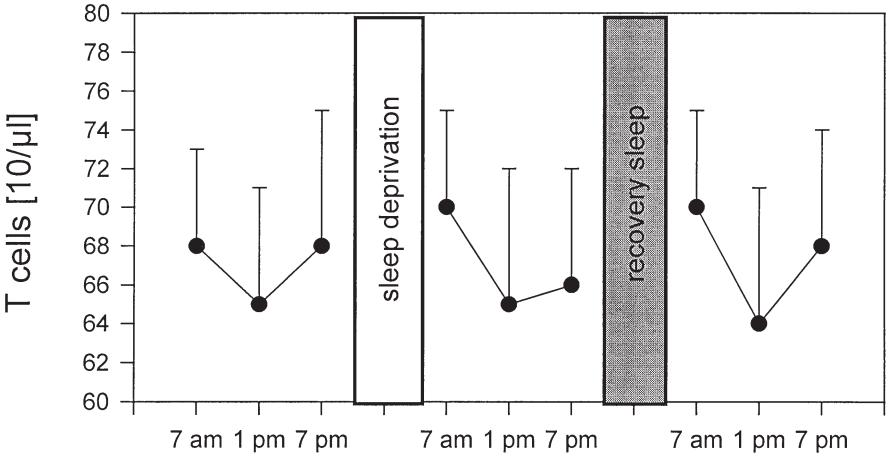

Fig. 6 Mean values (± standard deviations) of T cells before and after sleep deprivation as well as after recovery sleep

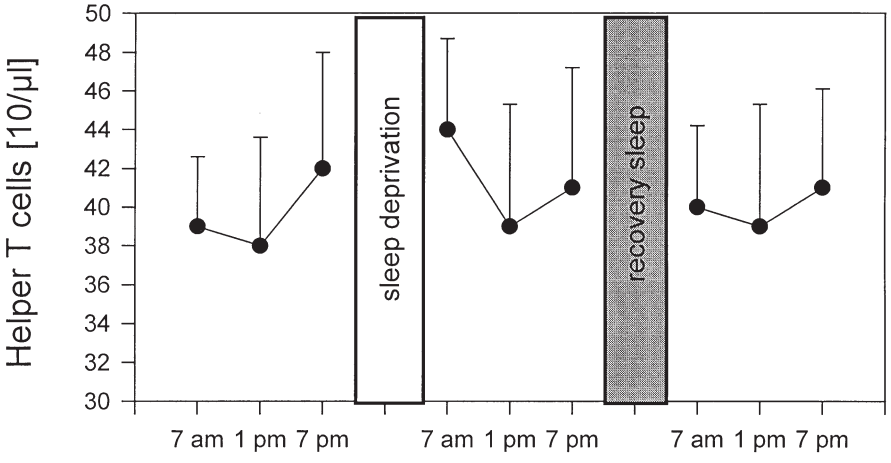

Fig. 7 Mean values (± standard deviations) of helper T cells before and after sleep deprivation as well as after recovery sleep

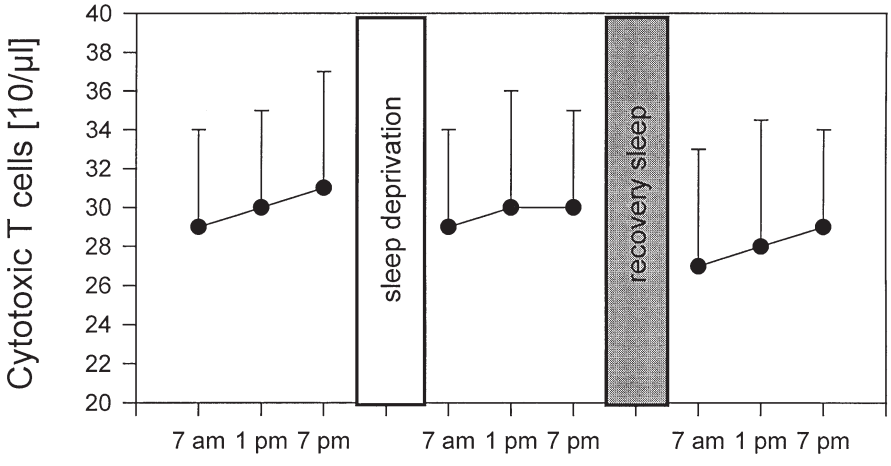

Fig. 8 Mean values (± standard deviations) of cytotoxic T cells before and after sleep deprivation as well as after recovery sleep

($p = 0.022$), monocytes ($p = 0.031$), T cells ($p = 0.005$), helper T cells ($p = 0.004$), cytotoxic T cells ($p = 0.005$) and NK cells ($p = 0.017$). Contrast analysis yielded significant differences between days 1, 2 and 3 for monocytes ($p = 0.017$) and NK cells ($p = 0.0001$). For all parameters that showed significant differences see Table 1. No significant interaction at all could be found for leukocytes, lymphocytes or B cells. The salivary cortisol rhythm was not affected by SD or recovery sleep.

Discussion

Most therapies for depression such as sleep deprivation (SD), pharmacotherapy, light therapy, electroconvulsive therapy (ECT), and psychotherapy lead to changes in the immune system. We therefore investigated SD, which forms an effective and rapid-onset therapy regime in depressives, and its effects on leukocyte subpopulation cell numbers.

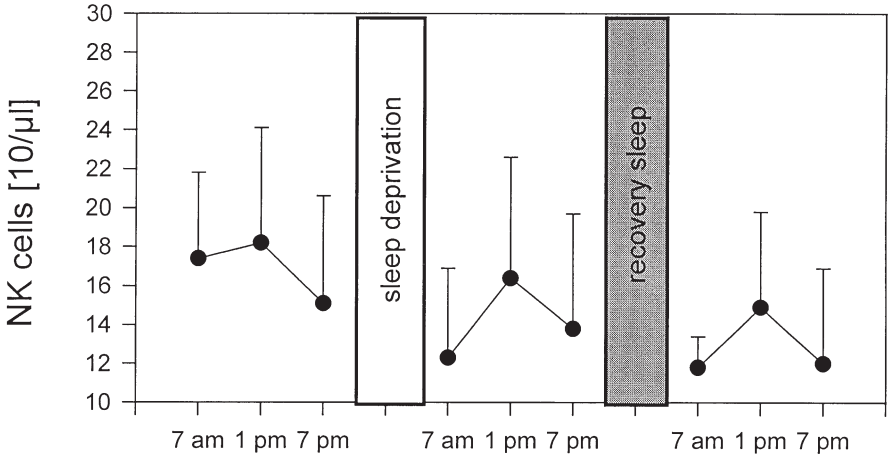

Fig. 9 Mean values (± standard deviations) of NK cells before and after sleep deprivation as well as after recovery sleep

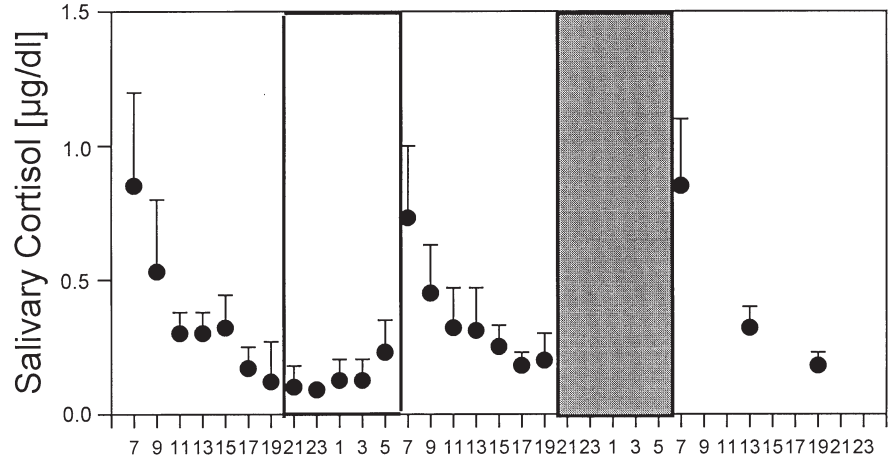

Fig. 10 Mean values (± standard deviations) of salivary cortisol before and after sleep deprivation as well as after recovery sleep

Since alterations in HPA axis activity have been demonstrated in many studies we investigated salivary cortisol.

In our study the NK cell number was reduced after SD at 7 am ($p = 0.001$). This is in line with the results of Dinges et al. (1994). The reduced NK cell number was consistent after recovery sleep. Given that depression is associated with elevated levels of NK cells (Ravindran et al. 1996; Seidel et al. 1996) this finding is quite interesting. A reduction of the reactivity of lymphocytes and of the NK cell activity in volunteers after SD was demonstrated in other studies. NK activity returned to baseline levels after a night of recovery sleep (Irwin et al. 1996; Moldofsky et al. 1989; Palmblad et al. 1979). The elevated NK cell number in depressives normalised with successful pharmotherapy (Ravindran et al. 1998). We also could demonstrate that the number of granulocytes was significantly increased after SD and recovery sleep when compared to 7 am values. Dinges et al. (1994) also found an increase in granulocytes after 64 h of SD. In our study monocytes, T cells, helper T cells and cytotoxic T cells yielded significant differences between single points in time across the day. Significant differences between days 1, 2 and 3 were found for monocytes and NK cells. No significance could be detected for leukocytes, lymphocytes, B cells and salivary cortisol after SD or recovery sleep. Dinges et al. (1994) found however a reduction in CD4 (helper T cell number), CD16, CD56 (NK cells) and CD 57 lympohocytes in contrast to unaltered other lymphocyte subpopulations after one night of SD. After stress and SD an increase in neutrophils and monocytes and a reduction of eosinophils and of all lymphocytes subgroups was seen by Boyum et al. (1996). Compared with sustained wakefulness, nocturnal sleep reduced the numbers of monocytes, NK cells, and counts of all lymphocyte subsets. However, in the afternoon and evening of the day following recovery sleep, counts of NK cells and lymphocytes were higher than after nocturnal wakefulness (Born et al. 1997). These studies were also performed with healthy controls. In our study salivary cortisol showed a daily rhythm with lowest values during SD. The cortisol rhythm was affected neither by SD nor recovery sleep which is probably due to the investigation of healthy controls. The results of plasma cortisol levels after SD in healthy volunteers in other studies are inconsistent. Brun et al. (1998) observed no difference in plasma cortisol during SD, recovery night, and control nights. On the other hand Vgontzas et al. (1999) concluded that SD results in a significant reduction of cortisol secretion the next day and this reduction appears to be, to a large extent, driven by the increase of SWS during the recovery

night. In depressives many alterations of the cortisol concentration were detected. Baumgartner et al. (1990) found increases in cortisol levels during the night of SD, compared to the night of sleep in depressives. The cortisol concentrations of the responders rose higher during SD than those of the nonresponders. The mean plasma cortisol levels of depressive patients tend to be higher than those of controls on the day following SD. In depressives the mean values of cortisol on the day following SD are higher compared to those on the preceding day. In the patients responding well to SD, the variation of cortisol mean values which was obscure the preceding day showed an evident rhythm the following day (Yamaguchi et al. 1978). Free urinary cortisol is found in larger quantities in depressives than in healthy controls and the amount of cortisol is again raised after a period of SD with a and simultaneous increase in amplitude (Goetze & Tolle, 1987). But there is no difference in cortisol levels of depressed SD responders and nonresponders before and after SD (Ebert et al. 1994). The diagnostic selectivity of DST results was not improved by combination with SD (Kuhs 1985). However the results of King et al. (1982) extend the positive association between an abnormal DST result and the antidepressant response to SD. In a study of Lee & Taylor (1983) five of ten patients with endogenous depression improved following SD. All five SD responders were pre-SD DST non-suppressors.

These results may indicate that the alterations of the immune system after SD, especially of the NK cells, lead to enhanced nocturnal plasma IL-1-like and IL-2-like activities (Moldofsky et al. 1989) since central administration of IL-1β suppresses NK cell activity (Hodgson et al. 1999). Insomnia is associated with a reduction of natural killer activity in depression (Irwin et al. 1992b). Plasma IL-1β is increased after SD (Krueger & Majde, 1995) and IL-1β is decreased during and after recovery sleep (Moldofsky et al. 1989; Dinges et al. 1995). The release of IL-1β from platelets after activation with serotonin was positively related to personally subjective ratings of experienced tiredness of volunteers after SD and recovery sleep (Heiser et al. 1997). Cortisol has also effects on NK cells. High plasma levels of cortisol reduce NK cells in vitro (Mandler et al. 1986). Bodner et al. (1998) demonstrated that a significant decrease in plasma cortisol levels was found along with a significant increase in NK cell activity in healthy controls.

Keeping in mind all the limitations of comparing healthy subjects with depressive subjects, our findings support the assumption of alterations in the host defence system after SD and recovery sleep. The detailed study of leukocyte subpopulations showed a significant reduction of NK cells and an elevation of granulocytes after SD as well as after recovery sleep. The cortisol rhythm was affected neither by SD nor recovery sleep in healthy subjects.

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