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Research report

Effects of sleep deprivation on sleep and sleep EEG in three mouse strains: empirical data and simulations

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Abstract

Gene targeted mice can be used as models to investigate the mechanisms underlying sleep regulation. Three commonly used background strains for gene targeting (129/Ola, 129/SvJ and C57BL/6J) were subjected to 4-h and 6-h sleep deprivation (SD), and their sleep and sleep EEG were continuously recorded. The two-process model of sleep regulation has predicted the time course of slow-wave activity (SWA) in nonREM sleep after several sleep-wake manipulations in humans and the rat [3,9]. We tested the capacity of the model to predict SWA in nonREM sleep on the basis of the temporal organization of sleep in mice. The strains differed in the amount and distribution of sleep and the time course of SWA. After spontaneous waking episodes of 10–30 min as well as after SD, SWA was invariably increased. Simulations of the time course of SWA were successful for 129/SvJ and C57BL/6J, but were not satisfactory for 129/Ola. Since the time constants are assumed to reflect the dynamics of the physiological processes involved in sleep regulation, the results provide a basis for the use of gene targeted mice to investigate the underlying mechanisms.

Keywords: EEG spectra; Two-process model; Mice

1. Introduction

With the progress in genetic engineering, mice are gaining importance in the neurosciences. Transgenic and knockout mice have become important models to investigate the contribution of genes to behavior. Such mice are useful also for the identification of genes involved in sleep, as well as for a better understanding of the mechanisms underlying sleep regulation (e.g., [13,48]).

There are several descriptive sleep studies in mice, but little is known about the mechanisms underlying the differences between strains. Early work demonstrated that some EEG and sleep traits are inherited both in humans and laboratory mice. Valatx et al. [53] showed that total sleep time (TST) and the ratio between paradoxical sleep and slow-wave sleep differed in several inbred mouse strains and their offspring. Recent ongoing analysis of quantitative traits has identified several loci in the mouse genome influencing the daily amount of non-rapid eye-movement (NREM) sleep and REM sleep [41]. Differences in sleep regulation and circadian activity in mice devoid of prion protein compared to wild-type controls indicated an involvement of the prion gene [25,46,48].

Since the early demonstrations of an increase in slow-wave sleep after SD in human [2], cat [52] and rabbit [32], studies in many other species including, rat, hamster, mouse, chipmunk, ground squirrel, dog, and dolphin, have shown increases in slow-wave sleep or slow-wave activity (SWA; EEG power density in the 0.75–4.0 Hz range) after SD. However, few studies have established a relationship between these changes and the duration of prior waking (cat: Ref. [26]; dog: Ref. [42]; rat: Refs. [5,21,43,44]). In human and rat this aspect has been most extensively investigated. It is well established for these species that SWA in NREM sleep is homeostatically regulated (reviewed in Ref. [4]). Thus, SWA is high at the beginning of the sleep episode, and thereafter decreases progressively. Moreover, SWA increases as a function of prior waking [12,43,44], and is lower at the beginning of the night following upon an afternoon nap [15,54]. Correlations between arousal thresholds and SWA in NREM sleep support the notion that slow waves represent an intensity parameter of NREM sleep (e.g., [20,31]). Also in support

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of this interpretation is the inverse relation between SWA and the number of spontaneous brief awakenings during sleep episodes [16]. Brief awakenings may serve as a behavioral index of sleep intensity, but it is unknown whether this applies also to mice. Although progress has been made in the understanding of the generation of SWA [38,39], in rodents the neuronal mechanisms underlying the transition from waking to sleep and the increase of SWA in NREM sleep after SD are still unknown.

The dynamics of sleep regulation have been simulated quite accurately for several experimental manipulations in humans with quantitative versions of the two-process model of sleep regulation [1,3,9]. This model postulates that sleep propensity is determined by an interaction of a homeostatic Process S, which is reflected by SWA in NREM sleep and a circadian Process C. A further attempt to use the model to understand these dynamics included the qualitative simulation of the polyphasic sleep-wake pattern, which is typical for rodents [9]. Subsequently, Franken et al. [19] performed a quantitative simulation based on an extensive data set obtained in the rat, consisting of a baseline day, 24-h SD and 48-h recovery. In contrast to the initial simulations for humans, where Process S decreased during both NREM sleep and REM sleep, in the rat Process S was assumed to decrease only in NREM sleep and to increase both during waking and REM sleep. A close fit between the time course of SWA and the simulated Process S was obtained [19].

Our aim was to test whether the two-process model can predict the time course of SWA on the basis of the temporal organization of sleep also in mice. Thus, we first investigated sleep regulation in three inbred mouse strains that are commonly used for gene targeting by subjecting them to 4-h and 6-h SD. We examined whether SWA in NREM sleep reflected the homeostatic Process S. The time constants of Process S were estimated on the basis of baseline data, and used in simulations to test whether they would predict the time course of SWA obtained after 6-h SD.

2. Materials and methods

2.1. Animals

Adult male mice, of three inbred strains were used: 129/Ola (Ola; $n = 9$), 129/SvJ (SvJ; $n = 6$) and C57BL/6J (C57; $n = 11$). They were maintained in a 12-h light–12-h dark cycle (lights on from 0800–2000 h; daylight-type fluorescent tubes, 18 W, 100–300 lx at the level of the mice), individually kept in Macrolon cages ($36 \times 20 \times 35$ cm) and placed in sound attenuated chambers. Food and water were available ad libitum. The animals were adapted for a minimum of 3 weeks to these conditions. Ambient temperature continuously recorded for 4-s epochs in four of the eight boxes during the three recording days was 22.5 ± 0.4°C.

2.2. Surgery

The mice were implanted with EEG and EMG electrodes under deep pentobarbital anesthesia (Nembutal sodium, 80 mg/kg i.p., volume approximately 0.5 ml). Two gold-plated miniature screws (Ø 0.9 mm) served as epidural EEG electrodes. They were placed over the right occipital cortex (2–3 mm lateral to the midline, 2 mm posterior to bregma) and the cerebellum (at midline, 1 mm posterior to lambda) and soldered to a plug with stainless steel wires. The EMG was recorded with two gold wires (Ø 0.2 mm) inserted into the neck muscle and soldered to the plug, which was anchored to the skull with dental cement. At least 3 weeks were allowed for recovery. Mean age in weeks at recording onset was (S.E.M. in parenthesis): Ola: 19.3 (1.0), SvJ: 17.2 (1.3), C57: 16.4 (0.8). The ages did not differ significantly (Duncan's multiple range test).

2.3. Experimental protocol and data acquisition

A 24-h baseline recording, starting at light onset preceded the 6-h SD. Mice were recorded during the SD and for the following 18 h (some of the 2-h baseline and 6-h SD data of the 129/Ola mice have been published previously in a comparison with 129/Ola prion protein knockout mice; Ref. [25]). At least 10 d later the mice were subjected to 4-h SD and recording continued for the remaining 20 h. SD began at light onset and was carried out by introducing objects (e.g., nesting material) into the cage, and later by tapping on the cages whenever the animals appeared drowsy or the EEG exhibited slow-waves. Halfway through both SDs the mice were given new cages, which provided additional stimulation and elicited exploratory activity. The mice were not touched during the deprivation, except during the cage change, and were never disturbed during feeding or drinking. The EEG and EMG signals were amplified (amplification factor ~ 2000), conditioned by analogue filters (high-pass filter: -3 dB at 0.016 Hz; low-pass filter: -3 dB at 40 Hz; less than -35 dB at 128 Hz), sampled with either 256 or 512 Hz, digitally filtered (EEG: low-pass FIR filter 25 Hz; EMG: band-pass FIR filter 20–50 Hz) and stored with a resolution of 128 Hz. EEG power spectra were computed for consecutive 4-s epochs by a FFT routine within the frequency range of 0.25–25.0 Hz. Between 0.25–5.0 Hz the values were collapsed into 0.5-Hz bins and between 5.25–25.0 Hz into 1-Hz bins. EMG signals were integrated over 4-s and ambient temperature inside the chambers was recorded at 4-s intervals. All data were recorded simultaneously and stored on optical disks. The EEG channels were calibrated with a 10 Hz sine wave, 300 μV_{PP} signal which was recorded before each experiment.

2.4. Vigilance states and analysis

Vigilance states were determined for 4-s epochs as described previously [46]. In short: waking: high EMG and low EEG amplitude and high theta activity (EEG power density in the theta band, 6.25–9.0 Hz) concomitant with irregular, high EMG values; NREM sleep: low EMG and higher EEG amplitude compared to waking, high SWA; and REM sleep: low EMG and low EEG amplitude, high theta activity. Epochs in which the vigilance state could not be identified were excluded (percent of recording time: Ola: 0.03 ± 0.02, C57: 0.04 ± 0.04, SvJ: none). Epochs containing EEG artefacts were marked and excluded from spectral analysis (% of recording time: Ola: 7.5 ± 0.8, SvJ: 5.5 ± 2.3, C57: 14.2 ± 3.4; more than 75% of all artefacts were in waking).

The duration and frequency of episodes was computed as previously in the Djungarian hamster [10].

Overall effects within a strain were analyzed by two-way ANOVA for repeated measures with factors 'time' (1-h or 2-h intervals) and 'condition' (baseline or recovery) with the exception of Fig. 3 where due to several 1-h values with no sleep, which result in missing values for SWA, a two-way ANOVA with factor '1-h interval' and 'condition' was used. Differences between strains were analyzed by two-way ANOVA with factors 'strain' and 'intervals'. Contrasts were tested by post-hoc two-tailed *t*-tests or Duncan's multiple range test only if the main factor or interaction of the ANOVA reached significance.

2.5. Simulation

According to the initial quantitative two-process model of sleep regulation, Process S consists of an increasing and a decreasing exponential process in waking and sleep, respectively [9]. We simulated the time course of Process S iteratively on the basis of the vigilance states as described previously [19]. In the 4-s epochs scored as waking or REM sleep, S increases as a saturating exponential function with an upper asymptote of 1, while in NREM sleep S decreases as an exponential function with a lower asymptote of 0. Time constants for the decrease (Td) and increase (Ti) were determined for each mouse and strain separately on the basis of the vigilance states of the 24-h baseline period.

S was computed according to:

increasing function: $S_{t+1} = 1 - (1 - S_t) \cdot e^{-\Delta t/Ti}$

decreasing function: $S_{t+1} = S_t \cdot e^{-\Delta t/Td}$

where t = 4-s intervals and $\Delta t = 4$ s.

Parameters were optimized by comparing hourly values of S and SWA in NREM sleep for the individual mice. Intervals containing less than 5% NREM sleep were ex-

Table 1
Distribution of vigilance states in three inbred mice strains in baseline and after 4-h (REC SD4) and 6-h (REC SD6) sleep deprivation

	129/Ola			129/SvJ			C57BL/6J		
	Baseline	REC SD4 ($n = 7$)	REC SD6 ($n = 9$)	Baseline	REC SD4 ($n = 4$)	REC SD6 ($n = 6$)	Baseline	REC SD4 ($n = 7$)	REC SD6 ($n = 11$)
WAKING									
L	36.4 (1.2)			33.1 (1.0)			35.9 (1.0)		
D	61.3 (1.8)a	56.3 (1.8)	56.1 (2.5)*	49.7 (2.7)b	43.3 (2.9)	45.4 (2.6)	66.9 (1.9)a	59.3 (2.7)*	57.1 (2.2)*
24-h	48.8 (1.4)a			41.4 (0.9)b			51.4 (0.8)a		
5–10 h	35.7 (1.9)	34.5 (2.7)		34.2 (2.6)	24.9 (0.3)*		36.7 (1.1)	31.2 (1.0)*	
7–12 h	37.8 (1.4)		32.6 (2.1)*	34.2 (3.1)		27.3 (1.8)*	37.8 (1.0)		30.0 (1.1)*
NREMS									
L	48.8 (0.9)a			57.2 (0.5)b			54.4 (0.7)c		
D	32.9 (1.4)a	35.5 (1.5)	34.3 (2.0)	44.5 (2.7)b	49.8 (2.2)	46.3 (2.3)	29.4 (1.6)a	34.7 (2.5)*	36.3 (1.8)*
24-h	40.8 (1.1)a			50.9 (1.2)b			41.9 (0.7)a		
5–10 h	48.8 (1.4)a	51.3 (1.9)		57.0 (2.4)b	65.6 (1.0)*		53.5 (1.6)ab	57.1 (1.6)	
7–12 h	47.4 (1.0)a		51.4 (1.8)*	56.1 (2.5)b		62.7 (1.8)*	53.1 (0.7)b		58.7(0.9)*
REMS									
L	14.9 (0.4)a			9.6 (1.0)b			9.7 (0.5)b		
D	5.9 (0.6)a	8.2 (0.5)	9.6 (0.7)*	5.7 (0.6)a	6.9 (0.9)	8.3 (0.3)*	3.6 (0.4)b	6.0 (0.5)*	6.6 (0.4)*
24-h	10.4 (0.5)a			7.7 (0.7)b			6.6 (0.2)b		
5–10 h	15.5 (0.6)a	14.2 (0.9)		8.8 (0.7)b	9.5(0.7)		9.8 (0.8)b	11.7 (0.7)	
7–12 h	15.0 (0.5)a		16.0 (0.6)a*	9.7 (1.1)b		10.1 (1.1)a	9.1 (0.5)b		11.1 (0.4)b*

Vigilance states expressed as percentage of recording time for the 12-h light (L) and dark periods (D), 24-h and, to allow comparison with recovery after the two SDs, hours 5–10 and 7–12 (hour 1 = first h after light onset). Recovery includes the first 6-h after 4-h SD (h 5–10) and 6-h SD (h 7–12) and the corresponding baseline 6-h value.

Values are means ($\pm$S.E.M.). a, b and c indicate strain differences based either on direct comparison of corresponding time intervals in baseline, or, after SD, comparing the difference BL-SD between strains (values with different letters differ significantly; $p < 0.05$; Duncan's multiple range test). * Indicate differences between the first 6-h interval or 12-h interval (D) after SD and the corresponding 6-h baseline resp. 12-h interval of the dark period ($p < 0.05$; two-tailed paired *t*-test).

cluded for calculation of SWA. Due to missing values, especially at the beginning of the dark phase, only 8 C57 mice were used for the estimation. The linear correlation between hourly baseline SWA in NREM sleep and the corresponding S value of each animal was optimized by varying the time constants and the initial value of S ($iV = S_0$) for each mouse, and searching for the best correlation (see Table 4 for highest *r*-values).

To test whether the estimated parameters could predict the time course of SWA, a simulation was performed over the entire data set consisting of baseline, 6-h SD which immediately followed the baseline day, and recovery. Simulations were based on 4-s data and the optimized parameters of each individual were used (Fig. 7). To enable the comparison between SWA and S, SWA was linearly transformed according to a linear regression based on the 1-h values. To compute a mean *r*-value over all animals, the data of the individuals was first Fischer-Z-transformed.

To compare the time constants between species, time constants were estimated also for the 24-h baseline data of male adult rats, which were published previously [37].

3. Results

3.1. Baseline

All strains were nocturnal. Nevertheless large strain differences were observed in the total amount of vigilance states and in the distribution over the light–dark period (Table 1; Fig. 1). Waking encompassed 50–70% of the dark period and sleep 60–65% of the light period. SvJ had the lowest 24-h level of waking, Ola the highest level of REM sleep. The largest light–dark difference in NREM sleep was seen in C57, the largest difference in REM sleep in Ola. Strain differences also were apparent in the episode duration and frequency of the vigilance states (Table 2). The frequency of all vigilance states was largest, and the duration of NREM sleep and REM sleep episodes shortest in Ola. There were also marked strain differences in the amount of brief awakenings (BA) (Table 3). In Ola BA were twice as frequent as in C57, while SvJ was intermediate.

Table 2
Episode duration and frequency of each vigilance state for the three strains

		129/Ola ($n = 9$)	129/SvJ ($n = 6$)	C57BL/6J ($n = 11$)
DURATION (min)	waking	5.0 (0.3)a	5.6 (0.2)a	8.6 (1.0)b
	NREMS	4.7 (0.1)a	7.1 (0.6)b	7.1 (0.1)b
	REMS	0.7 (0.0)a	0.8 (0.0)b	0.9 (0.0)c
FREQUENCY	waking	135.0 (6.8)a	101.7 (5.7)b	88.1 (8.4)b
	NREMS	150.4 (7.9)a	119.5 (8.6)b	95.8 (3.0)c
	REMS	210.8 (15.1)a	139.7 (15.4)b	109.9 (4.5)b

Mean 24-h baseline values (±S.E.M.; number of animals in parentheses). a, b and c indicate strain differences (values with different letters differ significantly; $p < 0.05$; Duncan's multiple range test).

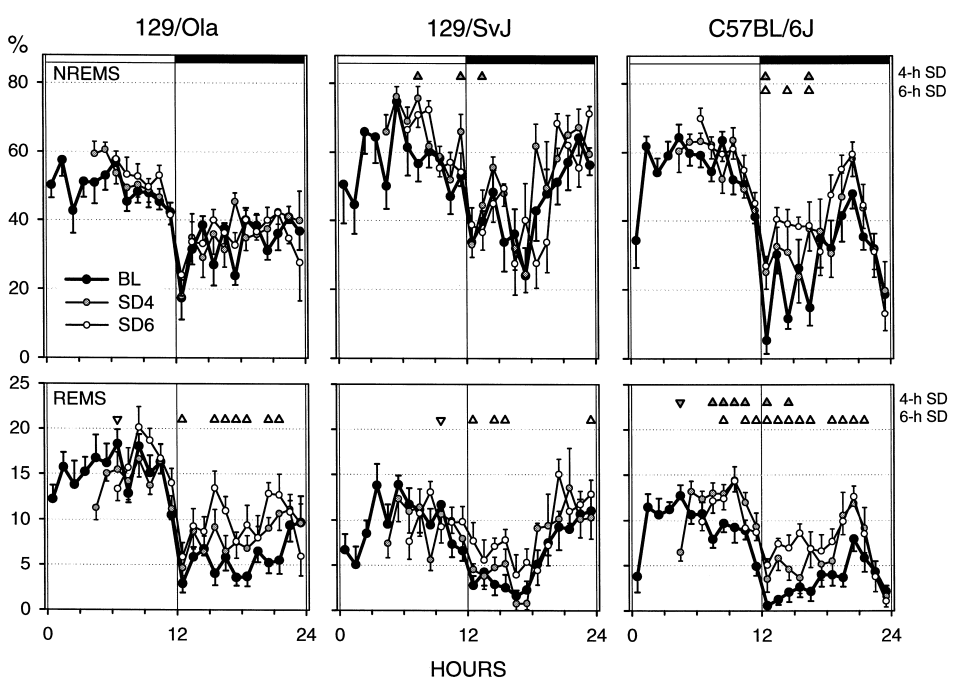

Fig. 1. Time course of vigilance states, non REM sleep (NREMS) and REMS for baseline (BL; 129/Ola $n = 9$; 129/SvJ $n = 6$, C57BL/6J $n = 11$), and recovery after 4-h and 6-h SD (SD4, SD6) for the three mouse strains 129/Ola ($n = 7$–9 for SD4 and SD6 respectively), 129/SvJ ($n = 4$–6) and C57BL/6J ($n = 7$–11). Curves connect 1-h mean values (±S.E.M.) expressed as percentage of recording time. In all strains 6-h SD resulted in a clear REM sleep rebound. Triangles indicate differences between recovery and corresponding baseline intervals, and their orientation indicates the direction of deviation from baseline ($p < 0.05$; two-tailed paired *t*-test, after significance in two-way ANOVA for repeated measures).

Table 3
Brief awakenings (BA) and slow-wave activity (SWA; EEG power density in the range of 0.75–4.0 Hz)

	129/Ola	129/SvJ	C57BL/6J
BA (< 16s)			
Baseline			
Light	56.8 (2.7)a	42.2 (3.6)b	26.5 (2.2)c
Dark	61.8 (4.9)a	45.9 (3.0)b	33.2 (3.0)c
24-h	59.3 (2.8)a	44.1 (2.3)b	29.8 (2.0)c
Recovery			
ΔSD4	−5.2 (3.5)	−10.7 (6.0)	−3.7 (1.4)*
ΔSD6	−12.9 (3.1)*	−7.7 (2.1)*	−5.1 (1.7)*
SWA			
Baseline			
Absolute power (μV^2)	186.6 (22.8)	255.8 (43.2)	230.2 (43.7)
NREMS/WAKING (%)	142.7 (7.5)a	119.9 (8.9)a	217.7 (25.7)b
Difference 24-h	30.2 (1.3)a	58.1 (5.2)b	54.0 (3.5)b
MIN–MAX value (%)			
Sleep deprivation			
SWA in waking (%)			
SD6/BL	149.6 (7.2)a*	101.2 (8.0)b	104.6 (9.6)b
Recovery (%)			
SD-corresp.			
SD4	49.9 (11.2)*	50.4 (33.3)	51.7 (5.6)*
SD6	53.0 (7.4)*	61.8 (9.6)*	55.2 (7.9)*
SD-24 h			
SD4	48.9 (11.8)*	41.5 (33.1)	41.0 (4.8)*
SD6	49.9 (6.3)*	48.3 (9.1)*	43.5 (6.4)*
SD-last			
SD4	39.9 (11.3)*	42.2 (33.7)	31.1 (7.9)*
SD6	45.4 (7.4)*	45.8 (11.6)*	28.2 (7.8)*

BA expressed as number per hour of total sleep time for the baseline 12-h light and dark periods and 24-h. The effect of sleep deprivation (SD) on BA is represented as the difference between the first 6 h after 4 and 6-h SD (ΔSD4; ΔSD6) and the corresponding 6-h baseline interval. SWA (μV^2): absolute SWA in the 24-h baseline, and SWA in NREMS expressed as a percentage of SWA in waking (NREMS/WAKING) and SWA in waking during the 6-h SD as a percentage of the corresponding 6-h baseline interval (SD6/BL). MIN–MAX: SWA difference between the lowest and highest 1-h interval. Three different calculations of the SWA increase after SD (Recovery) are presented as differences: 1. SD-corresp: first 1-h interval after SD — corresponding BL interval; 2. SD-24 h: first 1-h recovery interval — 24-h mean; and 3. SD-last: first 1-h recovery interval — last BL interval before SD.
Values are means (±S.E.M.; Baseline: 129/Ola $n = 7$, 129/SvJ $n = 6$, C57BL/6J $n = 11$; SD: $n = 7$, 4 and 9, respectively).
a, b and c indicate strain differences (values with different letters differ significantly; $p < 0.05$; Duncan's multiple range test). *Comparison between first 6-h recovery and corresponding baseline (two-tailed paired *t*-test; $p < 0.05$).

Total power in baseline computed over all vigilance states (Ola: 669.2 ± 77.9 μV^2, SvJ: 642.6 ± 67.2 μV^2, C57: 635.0 ± 120.4 μV^2) as well as SWA (Table 3) did not differ significantly between the strains (only those C57 mice were included in which the electrode implantation was performed by the same person, $n = 6$). In all three strains power in the range between 0.75–5.0 Hz was highest in NREM sleep, intermediate in waking and lowest in REM sleep (Fig. 2, bottom). However, strain differences were present. The difference between NREM sleep and waking, reflected in the ratio NREM sleep/waking was significantly larger in C57 compared to Ola and SvJ (Table 3), while the difference in EEG power in the lower frequencies between REM sleep and waking was similar in the three strains (Fig. 2). Although SWA decreased in the course of the light period, reaching a minimum towards the end of the light period, and rising again at the light–dark transition, strain differences were apparent (Fig. 3). In Ola SWA exhibited the smallest overall decrease, hourly fluctuation, and LD difference. This finding is reflected in the small minima–maxima difference within 24-h (Table 3).

3.2. Effect of sleep deprivation

SD affected the vigilance states and especially REM sleep (Table 1; Fig. 1). In Ola and C57 REM sleep was enhanced in the first 6 h after SD, and in all strains a rebound occurred in the 12-h dark following 6-h SD. In C57 a REM sleep rebound occurred also after 4-h SD. After 6-h SD the increase in REM sleep in C57 was due to a significant increase in REM sleep duration, while its frequency remained unchanged (mean duration in minutes: baseline h 6–12: 1.02 ± 0.04, first 6 h after SD: 1.25 ± 0.07; $p < 0.02$). NREM sleep was above baseline, at the cost of waking, in all strains in the first 6 h after 6-h SD. After 4-h SD an increase in NREM sleep in the first 6 h recovery was present in SvJ, and waking was not only reduced in the first 6-h, but still below baseline in the 12-h dark period in Ola and C57 (Table 1). Comparisons of the magnitude of the SD effects on the vigilance states (i.e., BL-SD) between the strains were not significant (Duncan's multiple range tests), with the exception of the REM sleep increase in the light period after 6-h SD which was largest in C57 (Table 1; 7–12 h).

After 6-h SD BA were significantly below baseline in all three strains (Table 3), while after 4-h SD a significant reduction was only observed in C57. The effects of 4-h and 6-h SD on BA did not differ within any strain (Ola: $p = 0.12$, SvJ: $p = 0.59$, C57: $p = 0.57$, unpaired *t*-test). The largest effect was observed in the initial recovery hours, both after 4-h and 6-h SD in Ola and 6-h SD in C57. None of the 1-h values reached significance in SvJ (Fig. 3). A tendency for a 'strain effect' was observed after 6-h SD (one-way ANOVA difference between strains of difference BL − 6-h SD; $p = 0.06$). The post-hoc test showed the largest decrease of BA in the Ola mice and the smallest in C57 ($p < 0.05$, Duncan's multiple range test).

The most prominent effect of both SDs was the immediate increase in SWA during recovery (Fig. 3; three-way ANOVA of the remaining 1-h intervals in the light phase after SD: factors 'strain', 'SD duration' and 'interval'; $p < 0.05$ for all factors). Due to the differences in the SWA time course during baseline, the initial SWA after SD was computed relative to the following three baseline values (Table 3): corresponding baseline interval, 24-h baseline mean and last value of the baseline dark period. In

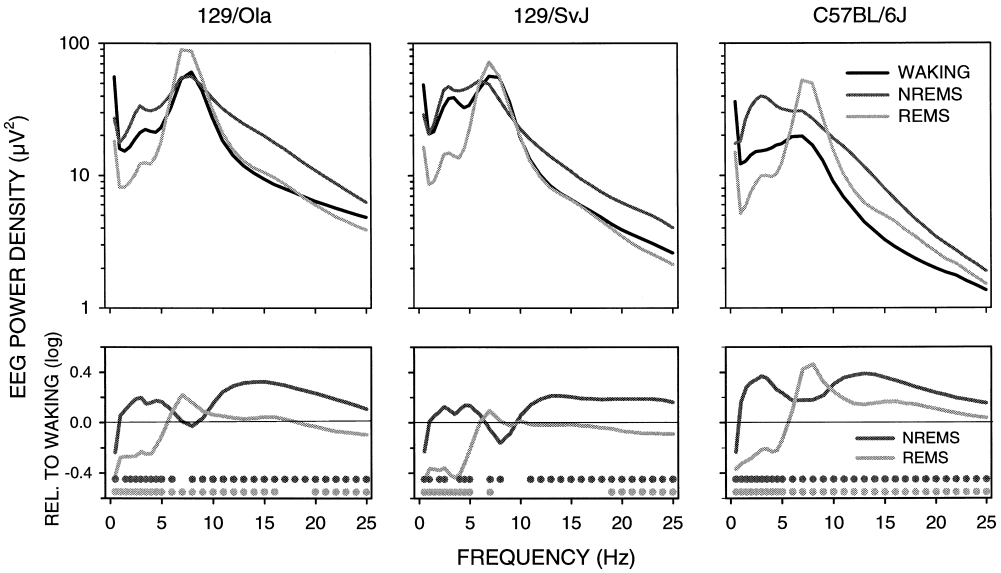

Fig. 2. Top: EEG power spectra in waking, non REM sleep (NREMS) and REMS. Mean absolute power values (μV^2/0.25 Hz) of the baseline light period on a logarithmic scale for the three mouse strains 129/Ola ($n = 9$), 129/SvJ ($n = 6$) and C57BL/6J ($n = 6$). Bottom: EEG power in NREMS and REMS relative to waking. Mean logarithmic ratio for each frequency bin. Dark (NREMS) and light (REMS) dots below the plots indicate significant differences from waking ($p < 0.05$; two tailed paired t-test after significance in two-way ANOVA for repeated measures). Values are plotted at the upper bin limit.

no case did the strains differ significantly in the SWA increase, but several differences were apparent in its time course. While the effect of 6-h SD subsided after 6 h in SvJ and C57, SWA remained above baseline for 11 h in Ola (Fig. 3). Moreover, in C57 SWA decreased below baseline in the late dark period after both SD conditions. In contrast, after 4-h SD, SWA was above baseline no longer than 3 h in all strains (Fig. 3). The entire spectrum shows that the largest increase of EEG power was between 0.75 and 5 Hz in all strains (Fig. 4).

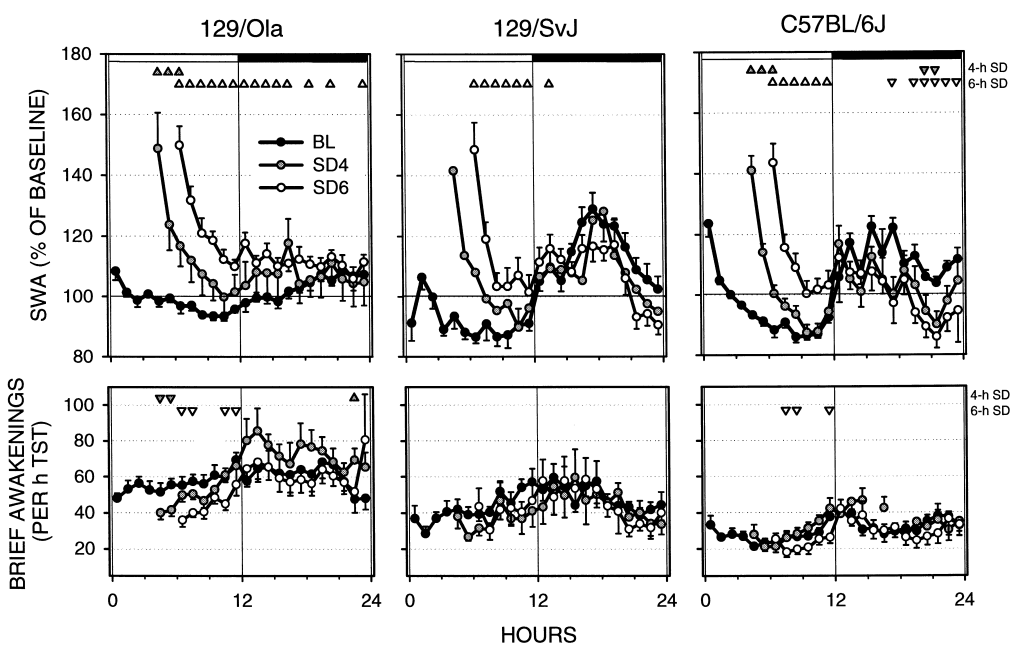

Fig. 3. Time course of slow-wave activity (SWA, EEG power density in the range of 0.75–4.0 Hz) and brief awakenings (BA) for the baseline (BL), and recovery after 4-h (SD4) and 6-h (SD6) sleep deprivation for the three strains. Curves connect 1-h mean values (S.E.M.; for details see legend of Fig. 1). SWA is expressed for every individual as a percentage of the 24-h baseline mean (= 100%) and BA as number per hour of total sleep time (TST). S.E.M. is omitted in SWA after 4-h SD in 129/SvJ (range of S.E.M.: 10.6–33.1). BA are lacking in some hours where little sleep occurred. Note the marked increase of SWA in all strains after 4-h and 6-h SD, and a reduction in BA after both SD's in 129/Ola only. Triangles indicate differences between recovery and corresponding baseline intervals. Orientation of triangles indicates the direction of deviation from baseline ($p < 0.05$; two-tailed paired t-test after significance in two-way ANOVA).

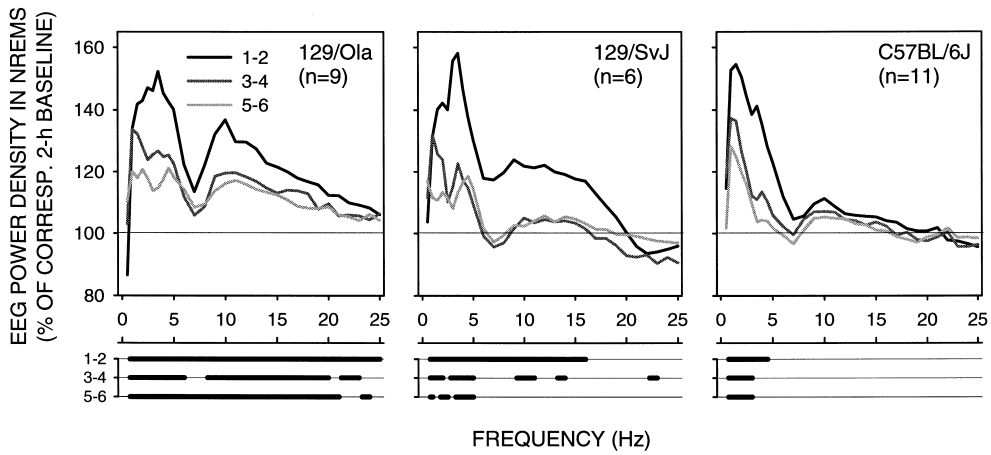

Fig. 4. Time course of EEG power density in non REM sleep (NREMS) in the light period after 6 h sleep deprivation for the three mouse strains. Values are plotted at the upper limit of each bin. Curves connect means of relative power density for consecutive 2-h intervals (1–2, 3–4, 5–6) expressed as percentage of the same bin in the corresponding 2-h baseline interval (= 100%). The common feature in all strains was the increase of EEG power in the low frequency bins, and its decreasing magnitude in the course of recovery. The horizontal bands below the abscissa indicate frequency bins which differed significantly from corresponding bins of baseline ($p < 0.05$, two-tailed paired *t*-test after significance in two-way ANOVA for repeated measures).

The relationship between SWA and BA was analyzed by computing correlations for the 1-h values of the baseline and recovery after 6-h SD. A negative correlation was found between the time course of BA and SWA for Ola (*r*-value = -0.31, $p < 0.05$), whereas the *r*-values for SvJ and C57 were not significant (0.13 and 0.11, $p > 0.2$).

To assess whether differences during the SD may have contributed to the strain differences in the recovery period, the EEG spectra of waking and NREM sleep were calculated for the SD intervals. This was hardly the case, since only short NREM sleep episodes occurred during the SDs (as % of deprivation time: SD4: Ola, 0.5 ± 0.1; SvJ, 0.5 ± 0.1, C57, 0.2 ± 0.1; SD6: Ola, 1.4 ± 0.4, SvJ, 1.0 ± 0.4, C57, 0.5 ± 0.2). SWA in waking was enhanced during the 6-h SD in Ola only. However, the lowest bin (0.75–1.0) was enhanced in all strains, both during 6-h (Fig. 5) and 4-h SD (not shown). In addition, power in waking in the frequencies above 8 Hz was above baseline during the entire SD in all strains (Fig. 5).

To investigate whether the effects of SD could be attributed to unspecific aspects of the SD (e.g., stress), the relationship between duration of spontaneous, undisturbed waking episodes during baseline and subsequent SWA was investigated for the light period (Fig. 6). Waking episodes were subdivided into 3 categories according to their duration (10–20, 20–30 and > 30 min). SWA was computed for the first 10-min of the subsequent NREM sleep episode and expressed relative to the 2-h interval where the waking episode began. A significant SWA increase was present already after 10–20 min of waking in all strains (Fig. 6;

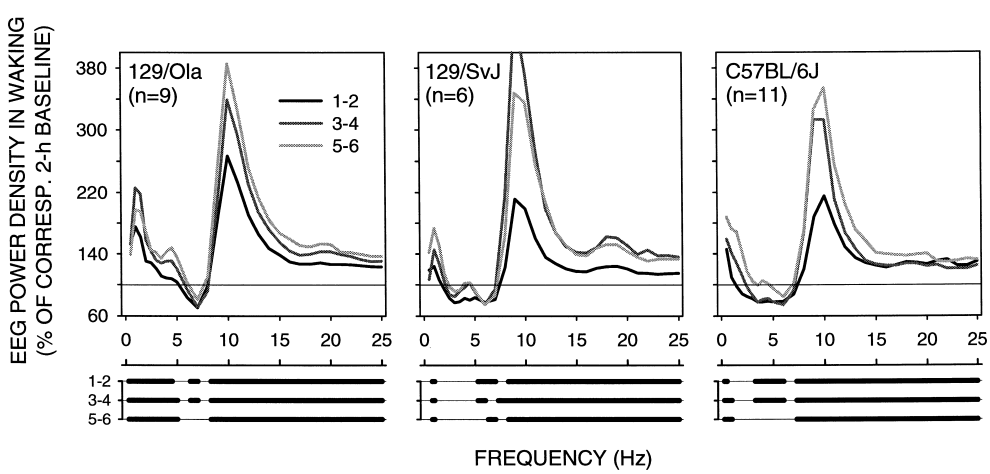

Fig. 5. Time course of EEG power density in waking during the 6-h sleep deprivation for the three strains. The horizontal bands below the abscissa indicate frequency bins which differed significantly from corresponding frequency bins of baseline ($p < 0.05$, two-tailed paired *t*-test). The value of the 8.25–9.0 Hz bin of the second 2-h interval in 129/SvJ was 444.75%. For further details see legend of Fig. 4. The most remarkable feature is the increase of power in the low frequencies in all three strains already within the first 2-h SD. The progressive increase in power in the delta range could indicate that it is reflecting sleepiness.

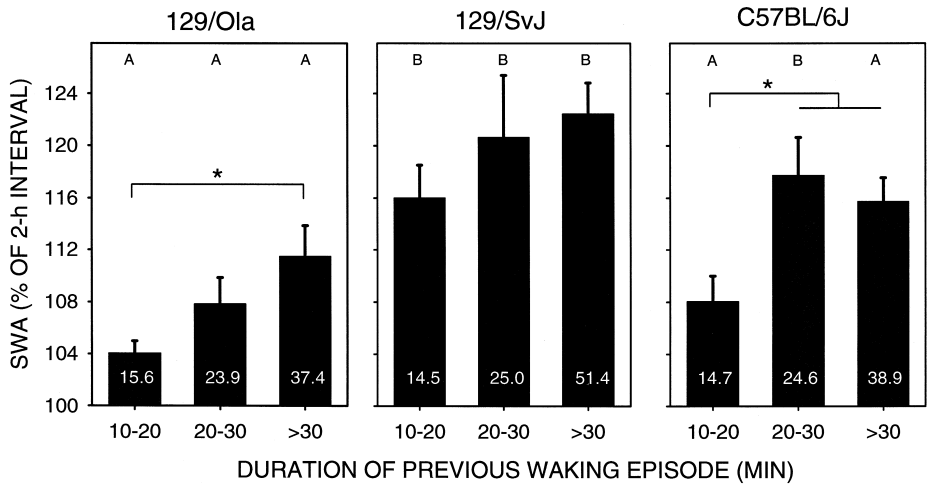

Fig. 6. Slow-wave activity (SWA, EEG power density in the range of 0.75–4.0 Hz) after spontaneous waking in the 12-h baseline light period. Waking episodes were subdivided into three categories according to their duration (10–20, 20–30 and > 30 min) for the three strains (n is as in Figs. 4 and 5). Numbers within the bars represent mean duration of waking contributing to the duration range. SWA increase in the 10-min non REM sleep (NREMS) immediately following the waking episode expressed relative to SWA in NREMS in the corresponding 2-h baseline interval. Already after 10–20 min of spontaneous, undisturbed waking all three strains show a significant increase of SWA. Two-way ANOVA factors 'strain' and 'waking duration'; $p < 0.005$ for both factors. Stars and connecting lines indicate differences in the increase of SWA within a strain ($p < 0.05$; Duncan's multiple range test). Letters above the bars indicate strain differences ($p < 0.05$; Duncan's multiple range test; bars with the same letter do not differ).

$p < 0.008$, paired t-test). After each of the three waking categories, SvJ had the largest SWA increase, with the exception of the 20–30 min category, where the increase in C57 and SvJ was similar. The comparisons within each strain showed a significantly larger increase after waking > 30 min than after 10–20 min in Ola and C57.

3.3. Simulation of slow-wave activity

To assess the validity of the homeostatic facet of the two-process model in mice, time constants for Process S were estimated for the baseline data and tested with the 6-h SD data. The estimated time constants Td and Ti and the iV (see Section 2 for definition) determined for the baseline records did not differ between SvJ and C57 (Table 4; $p > 0.3$, unpaired t-test). No meaningful time constant Ti could be obtained for the Ola strain, therefore no simulations were performed in this strain. In these mice Ti was highest compared to the other strains ($p < 0.05$, Duncan's multiple range test), but the range of Td and iV were similar to SvJ and C57.

The new parameter estimation for the rat data, which was computed exactly as for the mice, resulted in a significantly higher mean Ti than the one obtained for the SvJ and C57 strain, while Td and iV were in a similar range (Table 4). For comparison, the parameters previously published for the rat [19] and humans [9] are included in the table. The present estimation of Ti for the rat, which was based on baseline alone and on parameter optimization of individuals, resulted in a higher value than the one published by Franken et al. [19]. The latter was based on 4 consecutive days (baseline, 24-h SD and 2-d recovery), and optimized with the mean r-value over the entire group.

The simulation of Process S over the entire experiment with the parameters estimated for the baselines of the individuals (Table 4) resulted in a close fit between SWA and Process S for SvJ and C57 (Fig. 7). The fit was best in SvJ both for baseline and recovery. Some discrepancies between the simulation and SWA occurred during recov-

Table 4
Parameter estimation of the simulation of the time course of SWA during the baseline in three different mouse strains, and comparison to values of similar simulations in rats and humans

	Ti	Td	iV	r-value
129/Ola	25.9	11.2	0.38	0.78
($n = 9$)	(5.6)	(3.9)	(0.07)	(0.51–0.87)
129/SvJ	3.6	4.1	0.48	0.93
($n = 6$)	(1.1)	(1.0)	(0.10)	(0.86–0.97)
C57BL/6J	4.9	3.3	0.50	0.93
($n = 8$)	(1.2)	(2.1)	(0.11)	(0.82–0.97)
Rat new	13.5	4.1	0.57	0.86
($n = 9$)	(3.8)*	(1.1)	(0.10)	(0.47–0.93)
RAT[a]	8.6	3.2	0.55	0.79
HUMAN[b]	18.2	4.2	0.62	

Optimized initial value (iV) and time constants in hours for the decrease (Td) and increase (Ti) of the simulated time course of SWA. For each mouse strain and ''Rat new'', the variables represent the best estimation for the mean values (± S.E.M.) based on estimations of individuals (24-h baseline). Mean r-values: fit between data and simulation (range in parentheses).

[a] Ref. [19], estimation based on mean baseline, 24-h SD and 2-d recovery ($n = 9$).

[b] Ref. [9], * difference between rat (new) and 129/SvJ and C57BL/6J (Ola is excluded from the comparison; $p < 0.05$; Duncan's multiple range test).

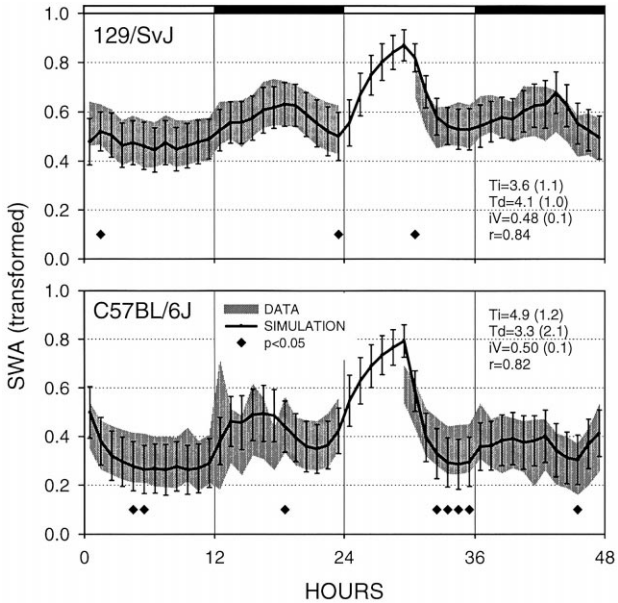

Fig. 7. Time course of slow-wave activity (SWA, EEG power density in the range of 0.75–4.0 Hz) and simulation with the optimized time constants for the increase (Ti) and decrease (Td) and initial value (iV) of Process S for 129/SvJ ($n=6$) and C57BL/6J ($n=8$). Curves and shaded bands connect 1-h mean values ($\pm$S.E.M.) for 24-h baseline, 6-h sleep deprivation and 18-h recovery. A close fit between the simulation of Process S and time course of SWA indicates that the two-process model of sleep regulation can predict SWA on the basis of the temporal organization of sleep also in mice. Diamonds indicate differences between simulation and data ($p<0.05$; two-tailed paired t-test). For the comparison between SWA and S, SWA was transformed according to a linear regression. Inset: mean values of Ti, Td and iV ($\pm$S.E.M.) and the mean r-value of the fit between SWA and S.

ery after SD in the C57. The simulation for the rat data applied to the 24-h baseline, 24-h SD and 48-h recovery [37], based on the individual estimated parameters for the rat baseline, resulted in a good fit between simulation and data with an r-value of 0.66 (not shown). When the correlation was performed with the mean 1-h values of the simulation and data the r-value was enhanced to 0.81.

4. Discussion

The results demonstrate that in all three strains, the increase of SWA in NREM sleep depends on the duration of previous waking. Although the initial level of SWA was similar after 4-h and 6-h SD, the increase persisted longer after 6-h SD [46,48].

The magnitude of the SD-induced SWA increase was similar between the strains (see also [18]). However, there is a clear species difference in the SD induced SWA increase. In the rat 24-h SD caused a slightly higher rise of SWA than 12-h SD [43], whereas in the mice an upper asymptote may be approximated already after 6-h SD, because there was only a minor increase of SWA from 4-h (50–52%) to 6-h (53–62%) SD (Fig. 3). In the C57 strain a 10-h SD ($n=5$) did not elicit an increase of SWA beyond the level of 6-h SD (data not shown).

A SWA increase occurred also after spontaneous, undisturbed waking episodes, and longer such episodes tended to be followed by higher SWA levels (Fig. 6). Also in Golden-mantled ground squirrels SWA was increased after spontaneous waking [27]. Enforced waking may entail stress [35], and stress does affect sleep (e.g., [22,29,34]), thus it could be argued that the changes after SD may be a consequence of stress. Our findings after spontaneous waking, as well as the results showing that no genes were differentially expressed after spontaneous waking for 3 h compared to 3-h SD in rats (reviewed in Ref. [7]), indicate that stress was not an important factor contributing to our data.

The increase of SWA already after spontaneous waking of only 10–20 min is consistent with the rapid increase of SWA to an upper threshold after a waking-NREM sleep transition in mice [17,46], and the slower increase in rat [51] and Djungarian hamster (Deboer, Huber and Tobler, unpublished). In these two species no such correlations were found (Deboer, Huber and Tobler unpublished). The inconsistent findings among rodents could be due to differences in the increase rate for SWA at the onset of a NREM sleep episode.

Our results indicate that there may be strain differences in the dynamics of the increase in SWA. We performed simulations of Process S to investigate whether the time constants would reflect these differences. A remarkable good fit between data and simulation was obtained for SvJ and C57, and their time constants did not differ. In contrast, in Ola the analysis failed to produce a satisfying result (note also the large standard error of the mean for Ti in this strain). The large time constant for the SWA increase (25.9 h) predicts that an upper threshold would be reached after approximately 3 days, exceeding the physiological range of spontaneous waking of a mouse. The problems with the simulations in Ola are a consequence of the small circadian amplitude in the time course of SWA during baseline (Fig. 3). The time constant estimation depends on the angle of the regression line resulting from the correlation between SWA and Process S. The flat SWA distribution results in a narrow angle close to zero, which gives rise to an extremely long time constant. Similarly, estimating the time constant in simulations of SWA in the guinea pig, which exhibits little SWA variation, were not successful [47]. Thus, the failure to obtain meaningful parameter estimates in Ola mice can be attributed to the mathematical limitations of the model.

The time constants obtained for SvJ and C57 could closely predict the effect of SD, including the negative rebound of SWA during the dark period in C57. A negative rebound has been observed previously in the rat after 24-h SD [14,16,21,37,50] and could be successfully simulated [19].

While the initial value (iV) and the time constant for SWA decrease (Td) for the rat was similar in the present study and a previous experiment [19], the time constant for the SWA increase (Ti) was longer. The present simulations were based on the time constants obtained for individual animals while Franken et al. [19] used means. The differences in Ti between the three species (Table 4), which diminish from 18.2 h in humans to 13.5 h or 8.6 h in rat to 3.6 h in mice, may be related to the corresponding decreasing duration of the sleep–wake cycles. In contrast, the process leading to SWA decrease (Td) seems to be more species independent (Table 4), varying between 3.2 h (rat) and 4.2 h (humans).

TST varied little between the strains, but marked differences were apparent in the distribution of sleep between the light and dark period, the ultradian sleep–wake pattern, and the time course of SWA between the strains. A large difference in the amount of sleep between the light and dark period results in a more prominent decline of SWA during the main sleep period. Thus, in the guinea pig, and in rats with lesions of the nucleus suprachiasmaticus which exhibit no circadian variation in sleep, the time course of SWA was almost flat [45,47,49]. The differences in the amount of REM sleep could be due to the presence of a major gene regulating REM sleep, which has been postulated on the basis of quantitative trait analysis of five mouse strains [41].

The mice showed a more prominent REM sleep rebound than other species. Thus, there may be a relationship between the effects of SD on REM sleep and species size. Thus, in the rat, 3-h, 6-h and 12-h SD resulted in a smaller REM sleep increase than the 6-h SD in the mice [43]. The REM sleep rebound was most prominent in C57. Since it has been shown that immobilization stress elicits a large REM sleep increase during recovery in the rat [22,34], it is possible that the differences in rebound between our mice could be a consequence of different underlying levels of anxiety. Behavioral tests have shown marked differences within 129 strains, including 129Sv and Ola, as well as compared to C57BL/6J [23,30,33]. However, it is premature to relate such differences to REM sleep, because the results of behavioral tests were not consistent and influenced by the laboratory environment [8]. Compared to other rodents only a small difference in power in the low frequency range between the waking and NREM sleep spectrum was present in the mice, and was the least in SvJ. Also Franken et al. [17] reported such differences in inbred mouse strains. It is still unknown whether these results are a consequence of differences in brain anatomy or physiological mechanisms, since the origin of slow waves in rodents is unknown.

Sleep was most fragmented in Ola (Fig. 3; Tables 2 and 3), and only in this strain a negative correlation of SWA and BA could be observed. In the rat [16], guinea pig [reference in Ref. [47]] and ground squirrel [40] BA were inversely correlated with SWA. In the mice, only after 6-h SD all three strains showed a significant decrease of BA compared to corresponding baseline intervals. This result may be related to the high values of BA encountered in these mice during baseline. In contrast, a minimal level of BA may not be lowered further by increasing sleep pressure. This interpretation is supported by the lack of SD-induced changes in BA in Djungarian hamsters, which have the lowest amount of BA among the rodents examined [11,24].

Some of the strain differences in the effect of SD may be a consequence of the significant increase of slow waves within the delta band in the EEG of the awake mice during the SD. In SvJ and C57 only the lowest frequency bin (0.75–1.0 Hz) showed an increase, whereas the changes in Ola encompassed the entire delta band. Such an increase has been shown also in rats in waking during recovery from 24-h SD [6], as well as in the course of SD [16]. Possibly SWA during waking reflects sleepiness, i.e., the pressure for sleep, indicating that Ola had a larger tendency to sleep during the SD. This was in agreement with our impression that Ola mice were more difficult to keep awake. How can this interpretation be reconciled with the low sleep maintenance in this strain? It seems that these mice can cope only with small changes in sleep pressure, reacting with an increase in SWA during waking already during the first 2-h SD. They had the smallest increase of SWA after spontaneous waking bouts and the most protracted SWA increase after 6-h SD. Thus, Ola was remarkable in several aspects. In all measures it had the largest fragmentation of sleep: high episode frequency, both of NREM sleep and REM sleep, and the largest amount of BA. In addition, these mice had the lowest 24-h SWA amplitude, which made it difficult to simulate Process S. This strain exhibited also several behavioral differences when compared with C57 or other sub-strains of 129 (e.g., [30,36]), however none of these differences provides an evident interpretation for the differences we observed in sleep.

Sleep regulation in humans and in the laboratory rat is predictable according to the tenets of the two-process model of sleep regulation. Our study shows that the model applies also to mice. The differences in the 24-h sleep–wake distributions between the strains, i.e., the temporal organization of the vigilance states, lead to accurate predictions of the time course of SWA. In view of the growing number of gene targeted mice, which are usually based on the 129/Sv and 129/Ola strain, and crosses with C57BL/6 it is important to investigate the cellular mechanisms involved in the generation and regulation of SWA in mice.

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