Sleep in the Blind Mole Rat *Spalax Ehrenbergi*

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Study Objectives: The mole rat, Spalax ehrenbergi, is an interesting species for sleep because of its pronounced specialization to a fossorial life. These rodents spend most of their life-time underground, and are less exposed to many of the environmental stimuli and challenges that are common to non-fossorial rodents. A prominent adaptation is their blindness, which is due to an atrophy of the eyes.
Design: Continuous 24-h recordings of EEG, EMG and cortical temperature, and EEG spectral analysis were performed in six individuals caught in the wild and adapted to the laboratory for several months.
Setting: N/A
Patients or Participants: N/A
Interventions: N/A
Measurements and Results: Total sleep time (52% of recording time) and the amount of REM sleep (8% of recording time) in these subterranean rodents are in the range of values found in the laboratory rat, mouse and hamster recorded under similar conditions. In contrast to these species, the polyphasic sleep-wakefulness distribution in mole rats was more distinct. A predominance of sleep in the dark period was only minor and not present in all individuals, which resembles sleep in the guinea pig.
As in all other mammals investigated, the daily time course of EEG slow-wave activity (SWA) in nonREM sleep closely followed the polyphasic sleep-wake pattern and the light-dark preference. The transitions from non REM sleep to REM sleep were characterized, as in other rodents, by a gradual increase in EEG activity in the theta and sigma frequency bands before the transition. However, the power surge in these frequencies massively exceeded that found in other rodents. This feature may be related to adaptations of the brain to the requirements of the subterranean habitat.
Conclusions: It is remarkable that large ecological differences between species within the same order have relatively small effects on many sleep features. The time course of SWA confirmed its predictability on the basis of the previous sleep-wake history.
Key words: Blind mole rat; EEG slow-wave activity; fossorial rodents; sleep; spectral analysis

INTRODUCTION

THE FUNCTION(S) OF SLEEP IS STILL UNKNOWN. Comparative sleep research makes use of the large diversity within mammalian species, both in their physiological and ecological features to identify the factors which determine the main properties of sleep in a species. Such a comparative approach has attempted to correlate ecological variables such as an index for predation, sleep exposure and overall danger as well as "constitutional" or physiological variables, body and brain size, metabolism, degree of maturity at birth and many others[1-4] with total sleep time and the amount of nonREM (NREM) sleep and REM sleep. In general, these variables could explain only approximately 60% of variance. On the other hand, a within species approach made use of the diversity of available mouse strains, and their progeny after cross-breeding to investigate the differences in the amount of sleep, its 24-hour distribution and homeostatic aspect of sleep regulation.[5-8] The order rodentia is especially suited for comparison because it comprises a large diversity of species, many of which can be maintained and bred under laboratory conditions. It is therefore not surprising that sleep has been investigated in detail in many rodents (e.g., hamsters, rat, mice, guinea pig, squirrels, and octodon degus).

The order rodentia comprises species which are specialized to their habitat. Some species exhibit major adaptations to a fossorial lifestyle (e.g., European mole, pocket gopher, solitary Cape mole rat and the blind mole rat; see [9]), where they are exposed only to small fluctuations in light and temperature. Sleep has been investigated in two species of moles, *Scalopus aquaticus* and a single specimen of *Condylura cristata*, both of which live underground, are known to be nearly blind, and feed on insects, worms and occasionally on plants.[10] These studies provided important data for the comparison with sleep in the echidna (spiny anteater, T*achyglossus aculeatus*[11]), a species belonging to a more primitive order of non-placental mammals, which also shows a highly specialized fossorial way of life. In the moles paradoxical sleep (or REM sleep) comprised 25% of recording time, the highest value for REM sleep found in mammals, shared only with the ferret, a carnivore, for which 24% were reported.[12] In contrast, no typical mammalian REM sleep was found in the echidna. However, recently Siegel et al.[13] showed that paradoxical sleep was not totally absent in the echidna, but that sleep in this species shows simultaneously features of both NREM sleep and REM sleep. This property can be explained by the very early stage in mammalian evolution of these egg-laying mammals. Thus, the vast amount of REM sleep in moles remains unexplained, and may be related to adaptations to its fossorial habitat.

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The blind mole rat *Spalax ehrenbergi* is a solitary, aggressive rodent, which feeds on roots and insects, mates in the winter, and exhibits many adaptations to a fossorial habitat.[14-19] Several studies have addressed the circadian system of Spalax, both in the laboratory and the field (e.g., [9,20]). Mole rats are totally blind, with a major atrophy of the eyes, which are covered by a furry skin. They do have some light-perception mediated by a functional cone-like pigment[21,22] and they are photoperiodic due to the hypertrophy of the SCN relative to the reduced number of ganglion cells.[23-28] To our knowledge, nothing is known about sleep in these animals.

We observed sleep behavior, and recorded the EEG, EMG and brain temperature (T_{CRT}) in several individuals after a prolonged adaptation to the laboratory. Spectral analysis was performed in order to characterize the EEG and the differences between vigilance states in detail. It was expected that the limited light-dark preference we had observed previously by recording running wheel activity in this species[9] would be reflected in the sleep-wake pattern and affect the daily time course of SWA (mean EEG power density in the 0.25-4.5 Hz band) in a similar way as in the guinea pig[29] and in the rat after lesion of the SCN.[30-31]

METHODS

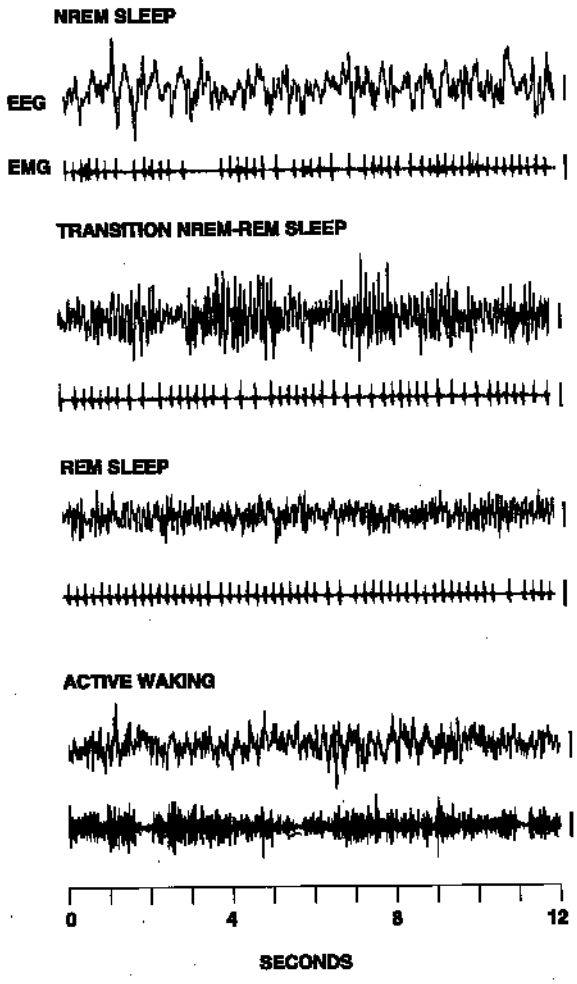

Figure 1—Representative examples of 12-sec intervals of nonREM sleep, a NREM -REM sleep transition, REM sleep and active waking for one individual. EEG and EMG (calibration bar at the left = 200 mV). Note: EKG was often superimposed on the EMG when the animal was asleep.

The present work was performed after approval of the governmental institution for animal experimentation.

Animals. Adult male mole rats (*Spalax ehrenbergi*) of unspecified age, captured in the field in Israel, transported to Zurich and adapted to the laboratory conditions for several months were used. Animals were maintained in a 12-hour light—12-hour dark cycle (lights on from 09:00-21:00h; daylight-type fluorescent tubes, 18W, 33-83 lux measured at the bottom of the cages), individually in aluminium cages (54x34x31cm), with sufficient wood chippings (approximately 10cm) to allow some burrowing. For recordings the cages were placed in sound attenuated chambers under the same light-dark schedule (5-25 lux). The animals were fed apples, carrots, and potatoes ad libitum. Ambient temperature continuously recorded for four-second epochs in the boxes was 20.6°C±0.2 SEM (n=6). The mole rats were provided with a running wheel (PVC, diameter 28cm), which was used vigorously.

Surgery. Mean weight at surgery was 136.7±9.4 g. The animals were first slightly anesthetized by metofane inhalation followed by Nembutal sodium (max. 50 mg/kg i.p., volume approximately 0.5 ml). Two gold-plated miniature screws (∅ 1.18 mm) served as epidural EEG electrodes. They were placed approximately over the right parietal cortex (2-3 mm lateral to the midline, 2-3 mm posterior to bregma) and the cerebellum (1-2 mm lateral from midline, 3-4 mm posterior to lambda).[33] Two additional screws served as anchors to fix the assembly to the skull. Screw fixation was difficult due to the extremely thin skull, especially over the cerebellum (recordings of two of the eight animals could not be scored due to artifacts caused by loose screws). Placing an assembly on the animal's head was avoided by connecting the screws directly to the cable leads without using a plug. In four animals a thermistor was inserted through a hole in the skull over the frontal cortex, so that the tip of the thermistor came to rest above the dura in the region contra-lateral to the parietal electrode. The EMG was recorded with two gold wires (∅ 0.2 mm) inserted left and right into the neck muscle and soldered to the cable leads. The cable was anchored to the skull with dental cement. At least two weeks were allowed for recovery and adaptation to the recording chamber. Due to the fine cables and swivel mechanism the animals were not obviously disturbed by the recording setup and their feeding and grooming behavior was not altered. The animals did not attempt to chew their cables.

Experimental protocol and data acquisition. EEG, EMG, and T_{CRT} were continuously recorded for a 24-hour period under the undisturbed conditions. In addition, the behavior of the animals was directly observed for several hours in the light period in every individual on separate days. To avoid disturbance of the animals, which perceived the presence of the observer, single mole rats were continuously recorded for several hours of the 12-hour light period on videotapes. During observations and video recordings the EEG and EMG were displayed on the PC monitor or on a polygraph. The EEG and EMG signals were amplified (amplification factor ~2000), conditioned by analog filters (high-pass filter: -3dB at 0.016 Hz; low-pass filter: -3dB at 40 Hz; less than -35 dB at 128 Hz), sampled with 256 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 four-second epochs by a FFT routine within the frequency range of 0.25-25.0 Hz. Between 0.25—5.0 Hz the values were stored as means for 0.5-Hz bins

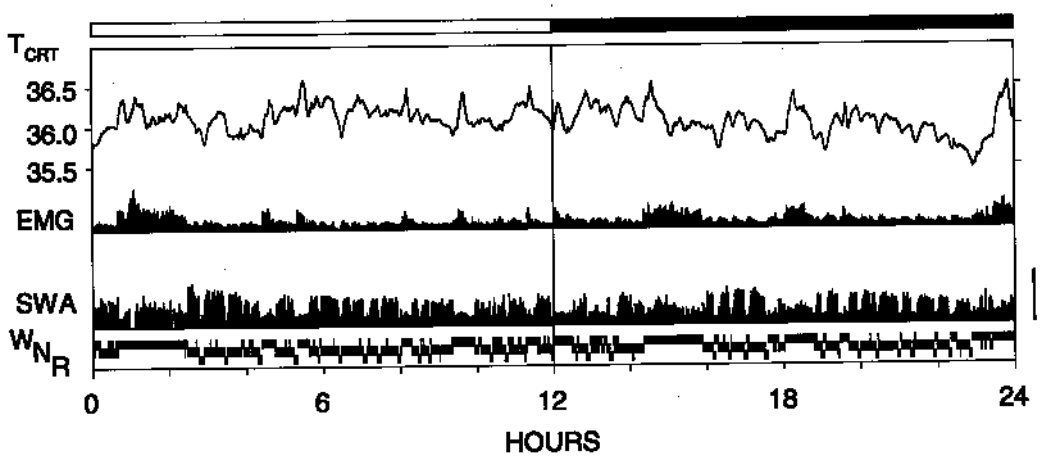

Figure 2—Continuous 24-h record of cortical temperature (T_{CRT}); °C SWA (mean EEG power density 0.75-4.0 Hz) and vigilance states (W, waking; N, nonREM sleep; R, REM sleep) of an individual mole rat. Each data point is the mean of 15 4-s epochs. EEG calibration mark (right) corresponds to 25 V^2/0.25 Hz. The light-dark cycle is indicated by the white and black bar (top).

and between 5.25-25.0 Hz for 1-Hz bins. EMG signals were integrated over four seconds. T_{CRT} and ambient temperature inside the chambers was recorded at four-second 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 immediately before the recording.

Vigilance states and EEG analysis. Despite burrowing in the wood-chippings the animals were always partially visible. The videotapes served to establish correlations between behavior and the EEG and EMG patterns before visually scoring the vigilance states. Thereafter, vigilance states were determined for four-second epochs based on the EEG and EMG. Epochs in which the vigilance state could not be identified were rare and were excluded (0.17%±0.13 SEM of recording time). Epochs containing EEG artifacts were marked and excluded from spectral analysis (30.8±8.7% of recording time). Most artifacts occurred during active waking (the total amount of waking was 48.2% of recording time, half of which was excluded from the spectra due to artifacts). In order to allow comparison with our studies in other rodents vigilance state episode frequency and duration were determined as previously (e.g., [8,34]).

RESULTS

The preferred sleeping posture was a tight curl perpendicular to the cage floor, with the head tucked (as far as possible) under the abdomen. When the animals engaged in motor activity, as determined by direct behavioral observation or post-hoc inspection of the video tapes, a typical waking EEG pattern with irregular, low amplitude waves concomitant with irregular, high EMG values was recorded (Fig. 1). Occasionally there was a discrepancy between behavior and the electrographic variables. The animals would display an EEG pattern which resembled either the waking (low EEG amplitude) or sleep pattern (high amplitude, predominantly slow waves) of other rodents, while the EMG did not change and the animal remained in a tight curl. Such epochs were scored as NREM sleep. The EMG in NREM sleep often showed a waxing and waning pattern elicited by breathing movements, and frequent small postural adjustments (Fig. 1). This was not the case during REM sleep. During waking, especially active waking, the overall neckmuscle activity predominated. REM sleep was scored when the EMG had consistently low values, except for the EKG which was in most animals superimposed over the EMG (Fig. 1). The EKG seemed to be less variable in epochs of REM sleep compared to NREM sleep, a feature which had been also noted by Allison and Van Twyver in moles.[10] In addition, at the transition from NREM sleep to REM sleep (as well as to waking), T_{CRT} increased abruptly (see Fig. 2). NREM-REM sleep transitions were gradual, usually characterized by several bouts of spindle like EEG activity (Fig. 1). During REM sleep behavioral twitches of feet and vibrissae, as well as irregular breathing were sometimes observed directly or on the video tapes. Total sleep time and the amounts of the single vigilance states are summarized in Table 1. The animals slept approximately 52% of the day, whereby REM sleep comprised 7.9% of recording time or 15.1% of total sleep time.

The mean 24-hour episode duration and frequency per hour (± SEM; n=6) was for waking 6.7±1.0 min and 4.7±0.7, NREM sleep 9.7±0.9 min and 3.0±0.2, and REM sleep 2.5±0.3 min and 1.9±0.1.

Brain temperature was 36.26°C±0.09 (n=4±SEM) over the 24 hours and slightly higher in REM sleep (36.27°C±0.07; see also Fig. 2) compared to NREM sleep (36.25°C±0.07). Brain temperature in the 12-hour light period (36.27°C±0.12) did not differ from temperature in the 12-hour dark period (36.26°C±0.09; $p<0.9$; two-sided paired t-test).

Spectral analysis of the EEG revealed differences between the three vigilance states. In the frequencies between 0.75-3.5 Hz absolute power in NREM sleep was significantly higher than in the other vigilance states ($p<0.05$; two-sided paired t-test), and in waking this band was intermediate between NREM sleep and REM sleep (Fig. 3). In contrast to NREM sleep, where there was no predominant, specific frequency band with a particular peak, REM sleep showed the typical peak in the theta frequency range around 4-6 Hz, which is well known for many mammals. Sigma activity (9-16 Hz) was manifested as a broad, relative peak within REM sleep, although the highest values in the sigma frequency range were present in NREM sleep.

Despite the small differences between the waking and REM

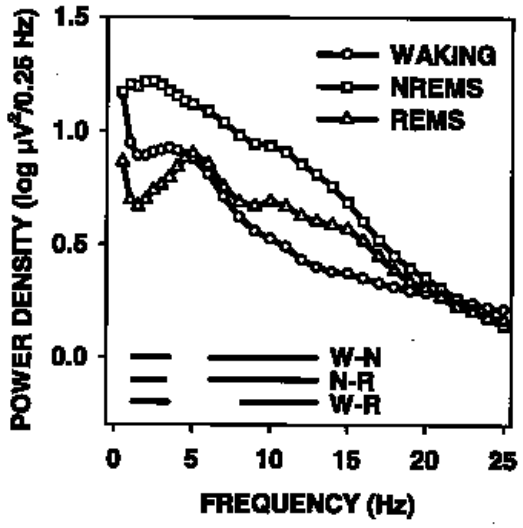

Figure 3—Spectral distribution of EEG power density during waking (W), nonREM sleep (NREMS; N) and REM sleep (REMS; R). The curves connect mean values per bin of the entire 24-h period (n=6). Values are plotted at the upper limits of each bin. The curves represent absolute values plotted on a logarithmic scale. Lines above the abscissa indicate the frequency bands for which the vigilance states differ significantly ($p<0.05$; two-tailed paired t-test after significance in the ANOVA factor "vigilance state").

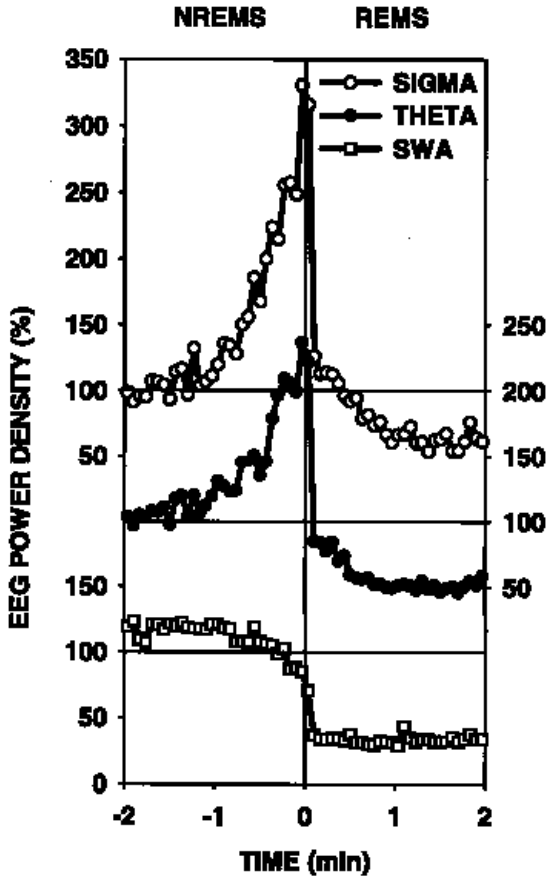

Figure 4—Time course of EEG power in three different frequency bands at the transition from nonREM sleep (NREMS) to REM sleep (REMS). Slow-wave activity (SWA, mean EEG power in the 0.75-4.0 Hz band), theta (6-9 Hz), sigma (11-16 Hz). The curves connect mean 4-s bins for 2 min before and 2 min after the transition (n=6). The curves are expressed as percentage of the 24-h value in nonREM sleep for the corresponding frequency band.

sleep EEG spectra, the transitions from NREM to REM sleep were usually clearly recognized during visual scoring of the EEG. The detailed post-hoc analysis of the time course of three EEG bands two minutes before until two minutes after the NREM—REM sleep transitions shows the gradual changes in the spectra during the transitions. In Fig. 4 it can be seen that especially the sigma (11—15 Hz) and theta (6—9 Hz) frequency bands showed a prominent increase relative to their respective mean 24-hour level in NREM sleep, which begins to raise slowly 60 seconds before the transition and increases gradually to a maximum. This activity could be seen in the raw EEG as spindle-like activity with very large amplitude (Fig. 1), and in most cases there was a gradual, marked increase also in activity in the theta band before the abrupt decrease in EEG amplitude at the NREM—REM sleep transition. Figure 4 (time 0) shows that this abrupt decrease was what led to the scoring of REM sleep.

All individuals showed a distinct polyphasic sleep pattern. In most individuals there were one to two waking bouts per day, lasting between one to two hours in which the animals engaged in burrowing, feeding and grooming (Figs. 2 and 5). Four mole rats were somewhat more awake during the light period than during the dark period (Table 1), but the LD-differences in vigilance states did not reach significance. One mole rat was indifferent to the LD-cycle and one was more dark active. The 24-hour distribution of REM sleep largely paralleled the distribution of NREM sleep (Figs. 5 and 6).

The time-course of SWA decreased in the course of the dark period (Fig. 6). The decrease was significant when SWA was computed for only those four mole rats which had a clear preference for sleeping in the dark period (ANOVA factor interval $p < 0.05$), the "main" sleep period, reaching the lowest daily values at the end of the dark period and remaining relatively low during the first half of the light period. A higher SWA value followed the decrease in sleep in the third two-hour interval, with subsequent lower values followed by an increase till the first interval in the dark.

DISCUSSION

The amount of sleep per 24 hours (51.8%) in the mole rats is higher than the one reported for moles (35.2%),[10] and is similar to the approximately 48% usually found in laboratory rats when they are recorded under similar conditions (e.g.,[35]). However, the lower values found in the moles recorded by Allison and Van Twyver[10] must be interpreted with caution, because those animals were described to be very susceptible to the laboratory environment and surgery.[10] The proportion of REM sleep relative to total sleep time in the mole rats (15.1%) is similar to the amount observed in the rat (18 %),[35,36] Djungarian hamster (15%),[34] and mouse (13%—20%)[8] recorded under similar conditions, but distinctly lower than in moles (25%).[10] Therefore, it becomes clear from our study that the large percentage of REM sleep (or "paradoxical sleep") reported for the moles, which are also fossorial and nearly blind, is not related to the degree of vision nor is it due to other specializations to the underground life. Both the duration of NREM sleep episodes (9.7 min compared to 4.7—7.1 min in different mouse strains, 5.2 min in rats, and 7.0 min in Djungarian hamsters), as well as of REM sleep episodes (2.5 min vs. 0.7—0.9 min in mice, 1.7 min in the rat and 1.8 min in Djungarian hamsters), was longer than in other rodents.[8,34,35] The

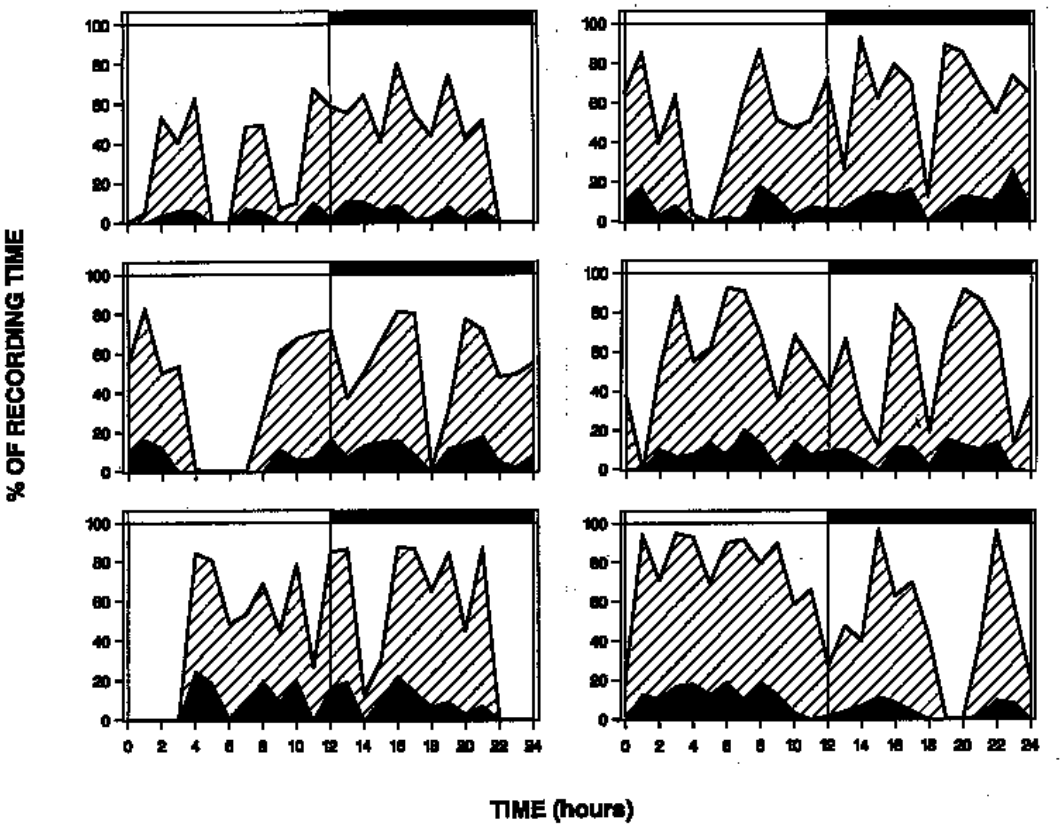

Figure 5—Distribution of the vigilance states waking (white area), nonREM sleep (shaded area) and REM sleep (black area) in each of the six individuals (mole rat number 1, 4, 5, left panels; 3, 2, 6, right panels). The 12-h light-12-h dark periods are indicated by the white and black bars at the top. The plots are based on 1-h values expressed as percentage of recording time.

Table 1—Vigilance states (waking; nonREM sleep=NREMS; REMS, total sleep time=TST as percentage of recording time and REMS as percentage of TST)

Mole rat	Interval	Waking	NREMS	REMS	TST	REMS/TST
1	Light	71.2	25.5	3.2	28.8	11.4
	Dark	52.8	42.3	4.9	47.2	10.3
2	Light	41.1	50.1	8.8	58.9	15.0
	Dark	45.1	45.7	9.1	54.9	16.7
3	Light	51.3	42.0	6.8	48.7	13.9
	Dark	34.0	54.5	11.5	66.0	17.4
4	Light	60.7	34.1	5.2	39.3	13.1
	Dark	44.3	44.9	10.8	55.7	19.4
5	Light	59.4	31.9	8.7	40.6	21.5
	Dark	44.1	46.6	9.2	55.9	16.5
6	Light	23.5	65.0	11.4	76.5	14.9
	Dark	51.6	43.6	4.8	48.4	9.9
	Mean 12-h light	51.2 (6.9)	41.4 (5.9)	7.4 (1.2)	48.8 (6.9)	15.0 (1.4)
	Mean 12-h dark	45.3 (2.7)	46.3 (1.8)	8.4 (1.2)	54.7 (2.7)	15.0 (1.6)
	Mean 24 h	48.2 (3.6)	43.9 (3.1)	7.9 (0.8)	51.8 (3.6)	15.1 (1.2)

Individual values of the six mole rats and mean 12-h and 24-h values (±SEM in parentheses). None of the 12-h values of the light period differed significantly from those of the dark period ($p>0.6$).

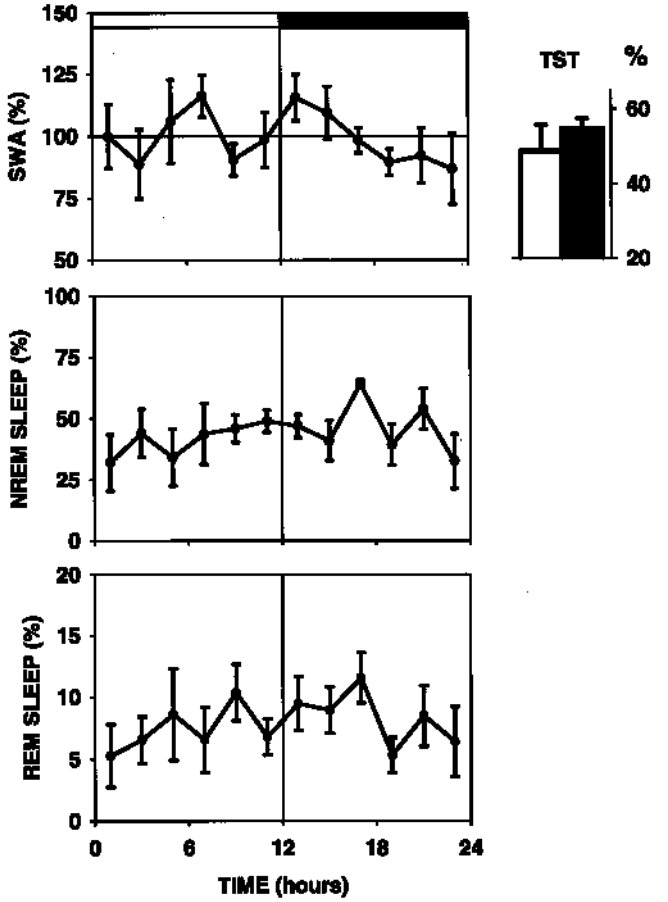

Figure 6—Mean±SEM (n=6 mole rats) 2-h values of slow-wave activity (SWA; mean EEG power density 0.75-4.0 Hz) in nonREM (NREM) sleep and the vigilance states NREM sleep and REM sleep for the 24-h recording. Light-dark cycle indicated at the top. Vigilance states are calculated as percentage of recording time. SWA is expressed relative to the 24-h mean of each individual. Right panel: Mean total sleep time (TST) ± SEM, as percentage of recording time, separately for the 12-h light (white bar) and 12-h dark (black bar) period.

echidna, the third species with a partially fossorial lifestyle, including poor vision, did not exhibit REM sleep epochs with the typical features found in other mammals.[11,13] The comparison between the species shows that the adaptations to the fossorial life-style, as well as the underground habitat have only a very small effect on sleep.

In contrast to the definition of vigilance states in other rodents (rat, hamster, mouse and guinea pig), where the waking and NREM sleep EEG patterns closely correlate with sleep and waking behavior, discrepancies were evident in the mole rats. Except for the intervals in which the animals engaged in vigorous motor activity, they remained curled up in a tight ball. During these prolonged "immobile" intervals the EEG either reflected the typical NREM sleep of other rodents, consisting of high-amplitude slow waves, or low-amplitude slow waves. Since we did not want to disturb the animals, we refrained from determining whether the low-amplitude NREM sleep was characterized by a lower arousal threshold. The comparison of the EEG spectra of the three vigilance states showed in most features a large similarity to the spectra in other rodents like the rat and Djungarian hamster. Nevertheless, in the mole rats the difference in the slow-wave range between NREM sleep and the other two stages was smaller compared to the rat and hamster. In this respect the spectra resembled those of mice, especially mice of the 129/Ola and 129/Sv strain.[8] Artifact elimination during active waking is an arbitrary procedure, because it is difficult to determine which EEG epochs are contaminated by movement artifacts. However, the similarity between the waking spectra in some mouse strains, which have little EEG artifacts and the mole rats renders it unlikely that the remaining waking spectrum was still to a large extent artifact contaminated.

The NREM—REM sleep transition showed the typical spectral changes we have reported previously for the rat, hamster, and mouse[34,37,38] after a similar analysis. However, in these rodents the surge of theta and sigma activity before the transition was much smaller whereas the increase in the mole rats was remarkable (Fig. 4). The EEG in the sigma band showed a more than three-fold increase and theta activity was up to 150% above the NREM sleep values immediately before the transition. In the rat the increase in the sigma band was only 30%—40 %[37,38] (10.25—20 Hz or 16 Hz, respectively) in an occipital derivation and less (15%) in a frontal derivation.[38] In mice of the 129/Sv strain an increase of 25% above the overall level in NREM sleep was present 30 s before the transition (Tobler, unpublished). In the Djungarian hamster theta activity increased by 25% at the transition,[34] while activity in the sigma range showed no particular change (Deboer & Tobler, unpublished). It is tempting to speculate that this prominent surge in sigma activity at the transitions in the mole rats may be related to adaptations of the brain to the fossorial habitat. Such a notion is compatible with the larger volume of the somatosensory cortex and somatosensory thalamic nuclei in mole rats compared to laboratory rats, after correction for differences in body size reported by Mann et al.[17] The peculiarity of the NREM-REM sleep transition, which is also evident in the visual inspection of the EEG has led some authors to score an additional "transitional" state (see[39], for a review). Figure 4 shows, that such a "state" is not homogenous, but consists of a gradual buildup of certain frequencies. Although the neuronal mechanisms leading to the transitions from waking to NREM sleep have been investigated in detail (e.g.,[40,41]).

The light-dark distribution of sleep, reflects the large variability between individuals observed previously in running-wheel activity recordings of a large number of mole rats recorded under similar conditions in our laboratory.[9] Despite the large inter-individual differences, the day-to-day variability in the light-dark distribution both of running wheel activity and activity measured by infra-red sensors was relatively stable within an individual. It is therefore unlikely that the variability in the sleep patterns of the mole rats reflects a regular day-to-day variation. It has been shown that SWA in NREM sleep closely reflects the previous sleep-wake history in animals and humans (for a review see [42,43]). In animals with a small or no preference for sleep in the light or dark period, which is typical for the guinea pig, or for rats after lesion of the SCN, SWA no longer exhibited the prominent decline encountered within the "activity" phase of the light-dark cycle in intact rats or in other rodents with a clear light-dark preference for sleep.[30-32] Similarly, in those four individuals, which were clearly more awake in the light phase, SWA exhibited a decreasing trend within the subsequent dark period. Although it was tempting to subject the animals to sleep deprivation to further investigate sleep regulation, we refrained from exposing them to the stressful procedures necessary for keeping them

awake. In the course of our studies stress reactions were evident, as soon as the animals sensed the presence of an observer, (e.g., when the cages were cleaned). They vocalized, moved backwards away from the stimulus and became very excited.

The sleep-wake pattern was markedly polyphasic, characterized by long bouts of sleep which were only rarely interrupted by prolonged intervals of activity (Figs. 2 and 5). Although it is obvious that the light-dark preference for sleep depends on light intensity in these blind animals, it is not evident why waking epochs were never particularly long. It has been postulated that the maximum length of spontaneous activity bouts in a species reflects its capacity to sustain arousal in the absence of environmental stimuli.[44]

In conclusion, the comparison of behavioral and polygraphic features of sleep in the mole rat with those of other rodent species show that sleep characteristics in rodents are remarkably invariable despite the large ecological differences between the species, including prominent adaptations to fossorial lifestyle.

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