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## 6. Comparative electrophysiology of sleep in some vertebrates

by M. Monnier

*(formerly Institute of Physiology, University of Basel), Äussere Baselstrasse 91, CH-4125 Riehen (Switzerland)*

An adequate investigation of the waking-sleep function in vertebrates requires, besides the comparative analysis of the behavioral manifestations, an electrophysiological quantitative analysis of the 24-h ‘circadian’ waking-sleep cycle, including the day (light) phase (07.00–19.00 h) and the night (dark) phase 19.00–07.00 h. The best approach is to follow the comparative evolutionist classification of vertebrates: amphibians (frog, toad); reptiles (lizard, turtle, crocodile); birds (starling, owl); mammals, as herbivores (rodents, cattle), insectivores (hedgehog), carnivores (cat, dog); primates (cercopithecoids, hominids); and man[1].

For the electrophysiological study of the waking state and sleep in animals, the same methods and criteria are used as for man. The electroencephalogram (EEG) is recorded concurrently with the electrooculogram (EOG) for quantification of the rapid eye movements (REM) during paradoxical sleep, in contrast to orthodox non-REM (NREM) sleep. For the same purpose, the ‘ponto-geniculo-occipital spikes’ (PGO) are recorded. The motor behavior is assessed by electromyography (EMG) and the visceral behavior (heart and respiratory rates) is under polygraphic control. An adequate quantification should involve waking (W) and total sleep (TS). Total sleep includes NREM and REM sleep. Orthodox NREM sleep is subdivided in man into initial stages (I and II) and later stages (III and IV). The latter are called slow wave sleep (SWS) or deep sleep. Paradoxical sleep (REM sleep) is characterized by initial PGO spikes, followed by a low voltage, high frequency EEG, rapid eye movements and loss of muscle tone. In higher vertebrates, the phase of rapid eye movements is associated with dreams.

### 1. *Amphibians*

Toads *(Bufo boreas; Hyla)* and frog *(Rana catesbiana)*. Investigations of Anurans *(Hyla* and *Rana)* showed that neither actually sleep. The tree toad *Hyla* has a more easily defined ‘resting phase’ than *Rana*; the EEG arousal threshold during rest is increased[2,3]. In *Bufo boreas,* 3 EEG and behavioral states were distinguished: a) Active awakened state, with maximal respiratory and cardiac rates; fast EEG frequency: 14–16 Hz; EEG amplitude: 10–40 µV; EMG: 15–20 µV. b) Relaxed wakefulness: animal motionless, yet responsive; reduced EMG amplitude (6–10 µV), as well as respiratory and heart rates; decreased EEG frequency and amplitude: 10–14 Hz, 5–10 µV. c) Resting behavior: animal unresponsive to external stimuli for 1–5 sec, relaxed posture; minimal respiratory and EEG activities: EEG: 5–7 Hz, 5–10 µV; EMG: 3–5 µV. The animals tend to be nocturnal; resting amounts to 87% in the photic phase and 24% in the scotopic phase. Thus, *Bufo boreas* does not exhibit real sleep, only a more pronounced resting state than the ever vigilant *Rana castebiana*[4].

### 2. *Reptiles*

A) Iguanid lizards *(Ctenosaura pectinata* and *Iguana iguana)* (n = 4). The weak EEG activity with small monophasic sharp and sawtooth waves during behavioral waking became polymorphic during behavioral sleep; the EEG decreased in frequency, but neither typical NREM nor REM sleep was recorded. Spikes and sharp waves reached peak levels (up to 385 µV) only during behavioral sleep. This association of spikes and sharp waves with behavioral sleep, without slow rhythms, in lizards, chelonians or crocodile reptiles indicates that sleep in lower vertebrates is not always correlated with slow-wave EEG, as in birds and mammals[5].

B) Tortoise *(Testudo denticulata).* 2 EEG states, unrelated to posture, were found : 1. State of fast, low voltage EEG (6–10/sec, 40 µV) with moderate EMG and heart rate. 2. ‘Spiking state’ with reduced EMG and heart rate. The high spikes (60–150 µV) were led from the olfactory bulb, cerebral hemispheres and optic lobe; they disappeared during behavioral arousal. There was no clear sleep[6].

### 3. *Birds*

In certain bird species (pigeon and hen), in spite of great differences in brain size and functional organization, slow-wave sleep occurs but paradoxical sleep is not prevalent.

Chief EEG stages of the waking-sleep cycle in mammals

| | Waking (W) | Total sleep (TS) | Orthodox sleep (NREM) | Paradoxical sleep (REM) |
|---|---|---|---|---|
| A) Percentage of 24-h experimental time | | | | |
| Rodents | | | | |
| Lesser short-tailed shrew | 36.6 | 63.4 | 57.5 | 7.9 |
| Insectivores | | | | |
| Hedgehog | 26.7 | 73.0 | 58.4 | 15.6 |
| Carnivores | | | | |
| Cat | 31.0 | 69.0 | 55.0 | 14.0 |
| Dog | 52.7 | 47.2 | 35.1 | 12.1 |
| *Homo sapiens* | 67.0 | 33.0 | 25.0 | 8.0 |
| B) Percentage of 12 diurnal h and 12 nocturnal h | | | | |
| Hedgehog | | | | |
| Day (light) | 16.3 | 83.7 | 63.6 | 20.1 |
| Night (dark) | 37.6 | 62.4 | 53.3 | 5.1 |
| Dog | | | | |
| Day (light) | 63.1 | 36.9 | 28.6 | 8.3 |
| Night (dark) | 41.8 | 58.2 | 42.1 | 16.2 |
| Primates | | | | |
| Cercopithecoids, *Papio* (dark) | 18.4 | 81.6 | 72.0 | 9.0 |

In this classification, NREM includes drowsiness, spindles-light sleep and deep slow-wave sleep. (B) demonstrates the necessity of distinguishing the EEG changes under daylight and dark conditions (12 h) in contrast to (A) (24 h). For birds, data on the complete (circadian) waking-sleep cycle were not available.

A) Starling and fowl (diurnal birds). In the starling, SWS occupied 38.3% of a 24-h period; only 46.2% of these SWS episodes were followed by REM sleep. The single SWS period lasted 4 min and the single REM epoch 16 sec. The sequence SWS-REM-AR (=arousal) appeared in 90.6% and the sequence NREM-AR only in 9.6% of the 24-h period. There was more REM sleep during the winter (resting period) than in spring and autumn (migration): 2.3% compared with 0.6% and 0.8% respectively. The sequence SWS-AR amounted to 53%[7].

In the fowl, during its short sleep periods, typical episodes of REM sleep with desynchronized EEG, rapid eye movements and loss of tone were observed.

B) Owl (nocturnal bird). The owl sleeps with claws holding fast to a tree branch; its EEG exhibits short REM periods (10 sec), but without loss of tone in the body muscles[8]. There are no rapid eye movements, because the eyes cannot move.

### 4. *Mammals*

In the mammals' waking-sleeping cycle, a certain unity is detectable. Species as different in morphology and behavior as mouse and elephant, cat, monkey and man, start resembling each other in their sleep patterns. Mouse and chimpanzee have sleep spindles almost identical in frequency. Nearly all mammals (mouse, rat, hamster, rabbit, cat, monkey) show an alternation of NREM and REM sleep[19].

*a) Small mammals, rodents.* The lesser short-tailed shrew *(Cryptotis parva)* is interesting for correlating sleep with body size. The chief stages were (mean for n=3): waking (W)=36.6%; drowsiness (D)=25.4%; TS=38%, divided into SWS=32.1%, REM=5.9%. This means that a very small body size is compatible with a fairly high amount of sleep[9].

The greater short-tailed shrew *(Blarina brevicauda).* The characteristics (for n=1) were: W=13.4%; D=24.4%; TS=62.4%, divided into SWS=52.6%, REM=9.8%. Thus, in the greater shrew, the amount of NREM and REM is higher that in the lesser shrew[10].

The Mongolian gerbil *(Meriones unguiculatus)* exhibits (in a series n=8) an amount of SWS+REM (63.7%) in 24 h similar to that of the shrew, with equal distribution of SWS for light and dark periods. By contrast, REM is higher in the light period. The gerbil appears to sleep more than the rat, hamster or mouse[11]; it is similar to the mouse in the amount of REM observed (REM/TS=10.9%)[12]. In mice, genetical studies showed that certain breeds exhibit no spindle sleep; other breeds have different durations of total sleep per day, different REM/NREM ratio and different reactions to changes in the light-dark cycle[13].

The cotton rat *(Sigmodon hispidus)* exhibits a typical rodent sleep (n=3): by light, TS=47% and the ratio REM/TS=13.1%. In the dark, the ratio REM/TS=6.3%, i.e. this ratio is lower than that of the golden hamsters of about the same size (~23%)[14].

In male Wistar rats (n=8), submitted to experimental quantitative EEG analysis during 4.5 h in daylight (morning), the following values were established: W=60%; TS=40%, consisting of NREM=35% (including spindles 5% and SWS 30%), and REM=5%[27].

b) *Lagomorph mammals.* Rabbit. Free-moving animals, adapted to daylight and laboratory conditions (n=10) provided, during 6 h, the following results:

W=60%, NREM=35%, REM=5%. The proportion of total sleep increases during the night[15].

c) *Insectivorous mammals.* Hedgehog *(Erinaceus europaeus).* The polygraphic results reported by 2 different teams revealed : W=26.7%, TS=17.6 h per 24-h period=73%, subdivided into 58% NREM and 15% REM sleep. By light, TS=83.7% (subdivided into NREM=63.6%; REM=20.1%) was longer than in the dark (NREM=53.3%, REM=9.1%). NREM consisted of drowsiness (DR) with spindles (10-12 Hz) during respiration pause and delta rhythms (3-4 Hz), followed by SWS (slow-wave sleep); concurrently, decreased reactivity to external stimuli and spikes in the hippocampus were observed. REM sleep was linked with body twitching, masticatory and eye movements, muscle atonia, low voltage high frequency EEG and a theta rhythm of 6-8 Hz. Waking (W) exhibited also 6-8 Hz theta rhythms in the cortex and the hippocampus, bursts of fast activity (40-60 Hz) superimposed on respiration-related slow waves in the olfactory bulb. The hedgehog has a high sleep quota, as have all hibernating rodents[16,17].

d) *Carnivorous mammals.* Cat. In the cat - widely used for experimental sleep research - the 2 phases NREM and REM sleep are easy to distinguish. The NREM sleep has typical spindles (12-14/sec), a high-amplitude slow delta rhythm and K-complexes. REM sleep is characterized by fast, low-voltage EEG activities, similar to those of the wakeful state, loss of muscle tone (generally recorded from the neck or chin muscles), body and limb jerks and rapid eye movements (REM). During this REM stage, regular theta rhythms (4-7/sec) occur from the hippocampus. POG spikes (ponto-geniculo-occipital spikes) also belong to the cat's EEG pattern in REM sleep; they are sharp waves, either single or grouped in bursts, from the pons, the corpus geniculatum laterale (relay nucleus of the visual pathway) and from the cortical visual field in the occipital lobe[18]. These PGO spikes occur a few seconds before the onset of REM sleep; they are correlated in time with rapid eye movements. Under laboratory conditions, sleep duration in the cat is about 16 in 24 h, with a predominance of day sleep[19].

Recent controls of the daily waking-sleep cycle of the laboratory cat showed that this animal is alert twice daily, at dawn and at dusk. The mean EEG values per 24 h are: W=31%; total rest+sleep=69%, subdivided into NREM=55% (DR=18%; SWS=37%) and REM=14%[20].

Dog. The stages of the circadian waking-sleeping cycle in laboratory dogs (n=10) have the following relative mean values: W=52.7%; TS=47.2%, subdivided into: NREM=35.1% (light sleep=20.7%; SWS=14.4%); and REM=12.1%. The percentage of the sleep stages was higher in the dark (d) than by light (l) at the cost of wakefulness. W: l=63.1 (d=41.8). TS: l=36.9 (d=58.2). SWS: l=10.5 (d=18.6). NREM (light sleep+SWS): l=28.6 (d=42.1). REM: l=8.3 (d=16.2)[21].

These results differ somewhat from those of a previous investigation: W=67.8%, TS=36.8%; NREM=23%; REM=8.7%[22].

e) *Herbivorous mammals (cattle).* Goats, sheep. Goats, after long laboratory adaptation, sleep a little; apart from NREM sleep, short REM phases are detectable[23]. In sheep, the REM percentage of total sleep reaches only 2-3%.

Ruminants do not sleep much, as suggested by their behavior. Ungulates, like horses, sleep longer, Thus, in the donkey, the sleep duration in 24 h reaches 13% of the EEG record[24].

f) *Primates (Cercopithecoids).* A series of adult *Papio Anubis* analyzed during 12 h provided the following values: W=18.4%; TS=81.6%, consisting of NREM=72% and REM=9%. In the NREM group, 4 stages were distinguished: I, II, III, IV[25].

Other reports on baboons, examined during 12 h, between 18.00 and 06.00 h gave the following values: W=14%; TS=86%, including NREM=76% and REM=10%[26].

*Conclusion.* A comparative electrophysiological analysis of sleep in vertebrates should be based on the evolutionist classification and apply to the whole 24-h circadian waking-sleep cycle. One should not assess only the duration of the various stages (waking, total sleep, orthodox sleep and paradoxical sleep), by night, but also their variations during the diurnal (light) 12-h period and the nocturnal (dark) 12-h period. A successful quantification is possible only in well preadapted, free-moving animals, submitted to remote EEG recording (telemetry) and automatic, computerized analysis. The lack of such modern techniques led to the previous conclusion that lower cold-blooded vertebrates do not actually sleep. A careful comparison of the EEG (spike discharges) and behavioral patterns with the anatomical brain organization corrects the impression that 'poikilothermic' amphibians, with inconstant body temperature and archaic brain, do not sleep, in contrast to homoiothermic mammals, with a more highly organized brain and EEG rhythms. This means that it is important to distinguish between an archicortical and a neocortical organization of the waking-sleep function.

From the table, A, it appears that the mammalian class is relatively homogeneous as concerns the waking-sleep EEG stages within 24 h. Rodents, insectivores (hedgehog), carnivores (cat) and lower primates *(Papio)* sleep about two-thirds of their waking-sleep cycle; during the total sleep period, the proportion of orthodox NREM sleep is high. In man, the proportions tend to be reversed: there is more waking, at the cost of NREM sleep. The domesticated dog exhibits the same tendency. A distinction between day and night conditions in the table, B, shows that the reversal of the waking and total sleep duration in dogs occurs only in the diurnal 12-h part of the circadian cycle. Many previous interpretations of the comparative data on sleep should be reconsidered according to the new technical requisites (telemetry) and to the concept of an integral waking-sleep function, influenced by the circadian biorhythm.

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## 7. Neural regulation of sleep

by Gian Franco Rossi

*Istituto di Neurochirurgia, Università Cattolica, Roma (Italy)*

One cannot understand and discuss the neural mechanisms underlying sleep without taking into account the mechanisms responsible for the physiologically opposite state of wakefulness. As we shall see below, both states depend on the functional interplay of 2 antagonistic cerebral neuronal systems. Obviously, under physiological conditions, the whole cerebrum participates in the sleep-wakefulness cycle. However, certain parts of it appear to be of paramount importance, so that the concept of an arousing (or activating) and of a hypnogenic (or deactivating) system is to a great extent justified. The 2 systems seem to be topographically concentrated in the brain stem with a rostral extension into the posterior diencephalon.

The neurophysiological research aimed at understanding the neuronal regulation of sleep and wakefulness was mainly based on the analysis of the effects of cerebral lesions and cerebral electrical stimulation. In both approaches neurophysiologists studied whether, and in which way, experimental manipulation of the brain affected the sleep and wakefulness behavior in animals. Or whether it affected somatic and visceral epiphenomena of the 2 states, or the cerebral electrical activity which, as is now well known, shows characteristic patterns for each physiological condition between the extremes of alertness and deep sleep. Modern sleep neurophysiology was heralded by the classical experiments of W.R. Hess (1927)[1] and Frederic Bremer (1935)[2]. Hess showed beautifully that protracted low rate electrical stimulation of the midline thalamus in the cat is followed by behavioral sleep; and Bremer demonstrated, also in the cat, that the transection of the neuraxis at midbrain level ('cerveau isolé' preparation) is followed by EEG patterns of sleep.

It was Bremer's experiment which, although later than that of Hess, prompted most of the experimental work on the sleep-wakefulness physiology during the following years. The sleep-like EEG patterns of the 'cerveau isolé' animal were ascribed to the suppression of an ascending influence with the function of keeping the cerebrum awake. In 1949, Moruzzi and Magoun[3] started a long series of experiments (see Rossi and Zanchetti[4] for references of the early work, and Moruzzi[5] for an excellent and exhaustive review) which showed that this ascending influence originates from the reticular formation of the rostral part of the pons and of the midbrain. Selective destruction of these brain stem regions is followed by a behavioral state of hypersomnia and by sleep-like EEG patterns, whereas their electrical stimulation at high frequency in the sleeping animal produces immediate arousal. This led to the hypothesis of the 'reticular activating system', i.e. of a cerebral neuronal system or circuitry responsible for the maintenance of the waking state. However, further experiments showed that if the 'cerveau isolé'[6-9] or the precollicularly decerebrated