Sleep Medicine 70 (2020) 6–16

Contents lists available at ScienceDirect

Sleep Medicine

journal homepage: www.elsevier.com/locate/sleep

Review Article

Relationships between REM and NREM in the NREM-REM sleep cycle: a review on competing concepts

Olivier Le Bon

Department of Psychiatry & Laboratory of Psychiatric Research (ULB 266), Cliniques universitaires de Bruxelles, Université Libre de Bruxelles (ULB), Bruxelles, Belgium

ARTICLE INFO

Article history:
Received 27 September 2019
Received in revised form
4 February 2020
Accepted 6 February 2020
Available online 15 February 2020

Keywords:
Ultradian
REM
NREM
Theories
Polyphasic
Monophasic

ABSTRACT

Sixty-five years after the discovery of rapid eye movement (REM) sleep, the reasons why we sleep and why we need two states of sleep are still largely unclear. Moreover, the functional relationship between the two types of sleep remains the matter of much conjecture. Several questions come to mind. How does sleep regulation in monophasic and polyphasic animals compare? What are the circadian and homeostatic influences on both states? Are non-rapid eye movement (NREM) and REM states dependent on each other, or are they regulated independently? What about long-term and short-term regulation? In addition, what determines the number and duration of cycles per night? What roles are played by temperature and energy allocation? The evidence collected over the years regarding these questions is summarized here, trying to address each issue.

1. Introduction

Since the discovery of rapid-eye movement (REM) sleep by Aserinsky and Kleitman [1], we have known that sleep is made up of two easily distinguishable neurophysiological states: rapid eye movement (REM) and non-rapid eye movement (NREM). Sixty-five years later, the reasons why we sleep and why we need two states of sleep is still largely unclear (see Refs. [2,3]). Moreover, the functional relationship between REM and NREM remains the matter of much conjecture. The two issues are linked. Uncovering their function(s) would help select between the rival hypotheses on their regulation. If REM and NREM regulation was better understood, precise tools could be used to challenge the competing hypotheses on their functions.

When an animal is not awake, the two sleep states alternate a number of times through the night (monophasic species) or during multiple sleep bouts over 24 h (polyphasic species). This switching back and forth of NREM and REM periods will be the main subject of the present review.

Crucial questions include the following. How does regulation in monophasic and polyphasic animals compare? What are the homeostatic and circadian influences on both states? Are NREM and REM dependent on each other or are they regulated independently? What about long-term and short-term regulation? Why is there more NREM sleep at the beginning of the night and more REM sleep at its end in monophasic species? How do the respective pressures for NREM or REM sleep express themselves in the final sleep pattern? What are the roles of body/brain temperatures and energy allocation? What determines the number and duration of cycles per night? Is there a true hourglass-like cycling or merely alternations? How do REM and NREM correlate with neuroanatomy and neurophysiology?

In the present paper, I will review the evidence collected over the years on these questions, trying to address each of these issues. I have chosen not to compare the merits of the mathematical models supporting the hypotheses. Although they constitute substantial arguments to support hypotheses when they can predict the pattern of actual nights, they are often complex to grasp intuitively and are difficult to compare directly with each other. It was deemed more novel at this stage to concentrate on primary logical and conceptual issues. In the Discussion section, I propose an asymmetrical solution to the issue of the ultradian cycling.

E-mail address: lebono@skynet.be.

https://doi.org/10.1016/j.sleep.2020.02.004
1389-9457/

2. Monophasic and polyphasic organizations of sleep: comparison and methodological issues

Endotherms, such as mammals and most bird species currently studied show the presence of both NREM and at least some REM sleep. Ectotherms only present with undifferentiated sleep and are not analyzed here (more on temperature below).

Most mammalian species are polyphasic sleepers, meaning that they sleep repeatedly for short periods throughout 24 h. Humans are part of the minority of monophasic sleepers, with a prolonged nocturnal sleep episode, or biphasic sleepers with afternoon napping. Cats have an intermediate status, showing several sequences of continuous NREM-REM alternations.

Rodents exhibit a typical polyphasic organization of sleep. About two-thirds of sleep episodes occur during daytime since most rodents are predominantly nocturnal. While humans present between 1 and 8 cycles per night (discussed later), rodents may show up to as many as 50–140 cycles over 24 h. The average number of cycles has been linked to the brain size of the species [4]. REM–REM cycle duration has also been linked to body mass [5].

In monophasic humans, deep sleep occurs primarily in the first half of the night, then decreases exponentially [6,7] a phenomenon that has no direct equivalent in rodents. REM episodes are also longer and more frequent at the end of human nights. Transitions between REM and subsequent NREM episodes in rodents include in most cases a brief waking interruption, which is not frequent in humans [8,9].

But as mammals are relatively close to one another in evolutionary terms, it seems likely that one basic explanation is valid for both types of organization. Anatomically and neurophysiologically, they also seem to share most elements of the NREM-REM alternation. Animal models can thus be used for detailed anatomical studies with immunological markers, optogenetic stimulation, lesions, sleep deprivation (REM-selective, partial or total), and manipulations of circadian influences.

Comparing human and rodents sleep can be done despite the presence of substantial methodological issues. Classifying rodent sleep into cycles over 24 h is more complex than in human nights. For instance, 25–50% of all rodent NREM episodes are not immediately followed by REM sleep, and about the same percentage of REM periods are not rapidly followed by NREM [10]. Since the number of REM periods is the index usually chosen for defining the number of alternations, many isolated NREM periods are included in the cycles when perhaps they should not be.

Also, NREM in humans can be divided into three gradual sleep depth levels: stage N1 (transition between wake and sleep), Stage N2 (light sleep) and Stage N3 (deep sleep, Slow Wave Sleep, SWS) [11]. Stage N3 is roughly the sum of the Stages S3 and S4 sleep used in the classification used until then [12]. Presently, there is no rodent equivalent of the NREM subdivision described in humans.

In terms of quantification (amplitude and incidence), Slow Wave Activity (SWA) is the only measure of NREM in rodents, whereas it only represents the SWS fraction in humans. It is thus an important part but not the whole of NREM, since N1 and N2 are not included. Also, because of potential amplitude differences of SWS, SWA is not a linear reflection of the NREM in which it is included. NREM, SWS and SWA thus represent similar concepts but are not synonymous.

In summary, although substantial differences must be taken into account, monophasic humans and polyphasic rodents, organizations of sleep probably share most elements of the NREM/REM alternations and one comprehensive theory should eventually explain both. These differences are important to keep in mind at a time where most of the studies on NREM/REM alternation are performed on rodents because the in vivo neurophysiological methods presently used would be considered too invasive on humans.

3. Classification of theories

It is helpful to our understanding of sleep cycling to make a distinction between long-term regulation and short-term regulation. For the purposes of discussion, long-term regulation includes homeostatic, circadian and allostatic influences. Short-term regulation, will refer to the relationships between REM and NREM within sleep, within a night (human adults) or over 24 h (rodents).

My present use of the concepts of long- and short-term differs from their classical use, which is focused only on homeostasis. This choice was made to allow for the possibility that long-term and/or short-term regulation is affected by other factors.

The distinction between long-term and short-term must not be overdone, because the two are necessarily intertwined. For instance, the Energy Allocation hypothesis [13] includes aspects from both. It proposes, among others, an integration of inputs from energy balance and sleep pressure, which can be considered long-term issues. At the same time, the ratio between REM and NREM is determined in part by the ambient temperature, a short-term consideration. This hypothesis will be studied separately.

4. Long-term regulation

Until the 1960s, sleep was mostly deemed to be regulated as a homeostatic process, either for the restoration of essential ingredients or for the detoxification of harmful substances [14,15]. After the discovery of REM sleep and based on sleep deprivation experiments, the sleep-wake cycle was instead hypothesized to be the product of two circadian oscillators. A stronger circadian oscillator, linked to REM and core body temperature (CBT), was supposed to interact with a weaker one, of longer periodicity, linked to the sleep-wake cycle [16]. Lacking plausibility, these two extreme models are now considered obsolete.

The two lines of thought were brought together by Borbély [17] in his famous two-process model (TPM). “A combination of the two principles seems ideally suited to allow the organism to generate compensatory responses to variations in its need for sleep, while confining sleep to the appropriate part of its daily cycle” [18]. The process S is derived from analyses of the spectral power of SWS, corresponding in spectral power to the delta band, or SWA. It represents the rising level of SWA propensity with the progression of waking. Process C corresponds to the circadian component of sleep propensity and is supposed to be controlled by a circadian oscillator unaffected by the occurrence of waking or sleep but linked to the CBT rhythm. The arithmetic sum of both processes determines the global sleep pressure. The model has since been quantified [18], extended [19], quantified and extended again [20]. Although since the early studies [17], attempts were made to integrate ultradian regulation and thus REM sleep [19,21], the TPM essentially addresses NREM sleep and SWA.

4.1. Homeostatic regulation of NREM

The amount of NREM deep sleep increases and sleep onset latency shortens as the previous waking time is extended [22–24,7]. Similarly, the total amount of stage 4 sleep was shown to be a function of previous partial sleep deprivation [6]. Sleep displacement studies, in which sleep was scheduled to daytime hours by varying the duration of previous wakefulness, have also emphasized the relationship of prior wakefulness to sleep propensity [25–29]. Sleep thus follows, at least in part, a homeostatic negative feedback, hour-glass type of mechanism, where its propensity

increases as a function of previous absence of sleep and accumulation of a sleep debt.

4.2. Homeostatic regulation of REM

Total sleep deprivation of approximately 40 h increases the amount of SWS while REM is not substantially affected [30,7]. Partial nonspecific sleep deprivation does not affect or increase SWS in recovery nights whereas REM tends to be reduced [31–33]. Selective REM deprivation experiments have shown a rebound in REM, and hence REM homeostasis [34–36]. Sleep extension (extra daytime sleep) reduces the amount of SWS in the subsequent night whereas REM is not much affected [37,38].

REM is thus more resistant to manipulations of sleep time than NREM and the time course of rebound is clearly different. For NREM sleep, the first recovery night may be sufficient for return to steady state [35,23,24], whereas REM remains elevated for several nights [34,22,23,39,35,40,24,41,42].

REM recovery after selective deprivation is thus a complex issue, moderate in duration, not particularly strong in the first recovery night but continuing across several nights. The REM recovery process appears to be slower, perhaps of lesser priority, but not necessarily of lesser importance, than NREM recovery.

4.3. Circadian regulation of NREM

In sleep deprivation protocols used to investigate circadian regulation on NREM, subjects are kept awake for prolonged periods of time. The results have shown that although sleep pressure monotonically increases throughout the deprivation period, it also exhibits pronounced, nearly 24 h rhythms, with peak alertness during the afternoon and peak sleepiness during the night [43,44]. A bimodal distribution of sleepiness was found, with a primary nocturnal peak and secondary peak at midday [45,46]. Sleepiness was confirmed to be maximal at early morning and minimal at early evening in constant routine protocols [47], an experimental procedure which helps control the influence of differences in light, human activity around the sleeper and motor activity.

4.4. Circadian regulation of REM

Isolation studies (time-free environment) are conducted in the absence of social and environmental time clues that may confound biological rhythms. Internal desynchronization was observed, with a close link between the CBT and REM rhythms at approximately 25 h, and larger oscillations from 15-20 h to 30–40 h in the sleep-wake cycle [33,48]. In forced desynchrony studies, subjects are isolated from all time clues. Somewhat shorter or longer “day” durations may be imperceptibly enforced on the subjects. An important finding from these studies was the failure to modify the CBT rhythm once the chosen day duration was too far apart from the usual 24 h, even if the subjects could adhere to the artificial light–dark schedules [49–51]. In most cases, the CBT rhythm began to cycle freely at its own pace, close to 24 h. Sleep propensity, sleep latency, sleep consolidation, sleep termination, sleep structure, distribution of REM and NREM episodes, NREM and sleep spindle peaks were all shown to be determined by their phase position relative to the CBT rhythm. A single pacemaker might thus be able to explain all observed circadian variations. This was confirmed in short- (eg, 90 min sleep, 3 h wake) and ultrashort (eg, 7 min sleep, 15 min awake) sleep period protocols [52,24,53].

4.5. Allostatic control

We have only a limited knowledge of how particular daytime variables influence NREM, REM, or both in humans. In real life, all kinds of stresses further complicate the issue. Allostasis makes up for various problems, such as in compensated heart, kidney or liver failures. The allostatic load is a measure of the physiological consequences of chronic exposure to fluctuating or heightened neural or neuroendocrine responses that result from repeated or prolonged stress [54]. The allostatic load has been shown to influence the quality of sleep significantly.

For instance, chronic stress was associated with more sleep apneas, increased severity of insomnia and shorter sleep duration [55]. For the moment, issues caused by allostatic load can be partially avoided by selecting healthy participants in sleep research. In future models, it will need to be integrated to complete the picture.

In summary, NREM and REM long-term regulations both present with a homeostatic and a circadian component. There appears to be a divergence in how the two states recover from sleep deprivation, with NREM recovery seeming to be a priority over recovery in REM. These homeostatic and circadian influences indicate distinct regulation rules for NREM and REM sleep, that may be further influenced by allostatic load.

5. Short-term regulation

5.1. Not a sleep-independent phenomenon

Could the alternation between REM and NREM within a night depend on a general clock mechanism? A common oscillator has been postulated to be responsible for several ultradian cycles of approximately 90 min, from genetic to endocrine to cognitive activity Basic Rest–Activity Cycle (BRAC) [56–58].

Several lines of evidence run against these hypotheses: (1) Short interruptions permit resumption and extension of the sleep cycle, whereas longer interruptions prompt a sleep cycle abortion, with a new cycle beginning after the onset of sleep [59]. After a certain duration of natural or experimental intermittent awakening, whenever the subject returns to sleep, a new sequence with a regular NREM-REM interval starts at the onset of sleep [60], [61,62]; (2) In spite of wide variations in bedtimes, sleep onset REM periods (SOREMPs) are exceedingly rare in normal human adults [63]; (3) positive relationships have been found between successive REM and NREM episodes, whereas if cycles were to begin at precise clock timings determined by forces external to sleep, one would expect negative links (see below). Consequently, all of the hypotheses described below are sleep-dependent.

5.2. Links between contiguous REM and NREM episodes

Fundamental to our understanding of the relationship between REM and NREM periods is whether links can be found with immediately preceding or immediately consecutive episodes of the other sleep state. Studies in rats [64,65], cats [66], monkeys [67,68], and humans [69] found predominant links between the duration of REM episodes and the duration of immediately consecutive NREM episodes. However, studies have also found correlations with preceding NREM periods, or a mixture of both in humans [70,69] (first cycle), cats [66] and rats [65,71]. A comparison between the duration/spectral power of NREM periods, and the duration of preceding and consecutive REM periods in humans, showed no clear general pattern [72]. The case seems stronger for polyphasic species than for humans.

Whatever the robustness of the relationship between REM and immediately consecutive NREM episodes, it has given rise to two quite distinct interpretations.

5.2.1. The REM episode duration determines the duration of the next NREM episode

As REM does not seem to be an urgent necessity for the organism [73], it is a great paradox that it invariably alternates with NREM and that efforts to prevent REM by repeated awakenings must increase throughout the night [34,31,74,75].

It was first hypothesized by Cox [76], that REM would help replenish and rejuvenate a weakening NREM (renewal hypothesis). Benington and Heller [64], proposed that REM pressure ("propensity") is a function of only the immediately preceding NREM episode, and not of a daytime, long-term REM homeostasis. REM pressure would be accumulated only during NREM and would increase progressively until some cofactor or neuromodulator reached a threshold and triggered the REM episode. REM would refuel NREM and allow for a delimited duration of NREM expression. There is no ultradian oscillator in this view. The REM sleep timing would be governed essentially by the accruing pressure during NREM. REM and NREM would share functions and be regulated as a whole.

5.2.2. The REM episode determines the interval to the next REM episode

The other hypothesis based on the relationships between a REM episode and its immediately consecutive NREM episode is that REM sleep has its own short-term homeostasis. What is left over from one REM episode is somehow memorized and discharged in a consecutive cycle, more or less independently of the NREM episode or wake occurring in between [65]. It is posited that REM and NREM pressures are accrued during daytime and respond to different functions.

5.2.3. Challenges to the "renewal" hypothesis

A study of rat subgroups deprived concomitantly of a similar 3 h REM but different (2 h, 1 h and 0 h) amounts of NREM showed no significant difference either in medians of REM rebounds or attempts to enter REM. The buildup of REM was thus inferred to be independent of the presence of NREM [77].

The effects of longer (24 h) and shorter (12 h) total sleep deprivation were compared: NREM recovery was only minimally different between the two experiments. By contrast, the REM recovery showed marked differences: after the longer sleep deprivation, there was a significant increase in successful attempts to enter REM and an increase in sustained REM episodes [71]. According to this author, REM pressure would be built during the other two states: wake and NREM. REM sleep would be governed by two homeostatic processes: a short-time pressure governing the timing of single REM periods and a long-term process setting the daily amount of REM sleep.

In summary, links between REM and consecutive NREM episodes must be confirmed but tend to support a short-term REM homeostasis and different functions for REM and NREM.

5.3. NREM-centered hypotheses

On visual inspection of all-night spectrograms in human sleep, SWA follows a series of peaks and troughs. It is tempting to see these SWA peaks as a manifestation of a pulsatile or endocrine process, where nadirs correspond to the end of sleep cycles [78,79]. In the One-stimulus [80] theory of NREM/REM alternation, the pulses increase SWA amplitude and density, depress arousal level and inhibit neural activity. When the strength of the pulsatile stimulus falls below a critical level, REM emerges as a neuronal escape.

Similarly, based on the observation that although REM is ubiquitous at birth, it is significantly diminished in adults and can be suppressed for quite long periods without obvious negative consequences, Horne [73], concluded that REM may be a "default" state, filling the gaps during NREM refractory phases in the absence of a need for wakefulness.

However, so far, no physiological substrate has been found that correlates to a spontaneously cycling SWA. Tentative models have failed to predict the occurrence and organization [81].

5.4. REM-centered hypotheses

5.4.1. Reciprocal Interaction (RI) and Limit-Cycle Reciprocal Interaction Model (LCRIM)

The first major breakthrough in mapping the circuits that underlie REM sleep commands was in 1975 [82]. Two groups of brainstem cells (Gigantocellular Tegmental Field [FTG] and Locus Coeruleus [LC] cells) were shown to discharge in parallel with the presence and absence of REM. FTG cells were labeled as "REM-on" and LC cells were labeled as "REM-off" cells [83]. These two groups of cells would constitute a functional dyad, acting together as one oscillator, responsible for the REM command (if not necessarily the REM behavior). Based on this functional oscillator, the Limit-Cycle Reciprocal Interaction Model (LCRIM) explains REM periodicity without direct reference to NREM.

The histological basis of the REM-generating command was later extended [84], as additional REM-off cells were found in the dorsal raphe (DR), and new REM-on cells were found in mesopontine laterodorsal and pedunculopontine tegmental nuclei (LDT/PDF).

Homeostatic regulation of the SWA module was integrated in the model that follows the rules of the two-process model. In the LCRIM, the REM-triggered signal powerfully antagonizes SWA and eventually disrupts it, leading to actual REM sleep. This accounts for the "skipped" REM episodes, where attempts to enter REM sleep are not followed by actual REM behavior.

A modulating "E" component was later added. This component represents noise in diverse forms: macro (awakenings) and micro (variations in SWA spectral intensity). The E component would stimulate REM-off cells and postpone the return of the REM cycle. One of the issues with the limit-cycle model is that intermittent awakenings delay the consecutive REM episode. The introduction of an E factor adds flexibility to this otherwise rigid pattern [85,21].

5.4.2. The NREM/REM flip-flop model (Mutual Inhibition, MI)

Decisive advances have since been made on the neuroanatomical side. The ventrolateral part of the periaqueductal gray matter (vlPAG) and its adjacent lateral pontine tegmentum (LPT) have been shown to contain many neurons expressing the orexin-2 receptor (ORX, orexin is also called hypocretin). Complete lesions of either of them doubled the number and duration of REM sleep bouts [86]. LPT lesions also caused occasional episodes of SOREMPs, cataplexy-like states and atonia [86]. Further analyses have refined the LPT zone into the deep mesencephalic reticular nucleus (DpMe). The vlPAG and DpMe are presently considered to be the main REM-off zones.

These REM-off areas provide intense projections into an adjacent region of mesopontine tegmentum, including the sublaterodorsal nucleus (SLD) and the precoeruleus (PC) region. Reports have shown that stimulation of GABAergic SLD and PC cells increase REM-like behavior [87–89]. Their lesions caused REM sleep to be markedly diminished, with very short bouts and an increase in the number of NREM-REM transitions, often leading to an awakening [86]. Further analyses [90], refined and extended the PC zone into the ventral medulla (vM) and the dorsal medulla

(dorsal paragigantocellular nucleus, DPGi). SLD, vM and DGPi are now considered to be the main REM-on zones.

Synaptic interactions were found between inhibitory REM-off and REM-on cells. Activation of REM-off vlPAG/DpMe strongly suppressed REM [90,91]. Inhibition of these REM-off cells increased REM [91]. Activation of REM-on SLD and vM neurons strongly promoted REM [90].

This circuit arrangement permits a mutual inhibition (MI) between REM-off and REM-on neurons [86]. By analogy to a sophisticated electrical switch, a flip-flop switch arrangement had been proposed by Saper et al. [92], to explain the switching back and forth between sleep and wake. In such a model, each group of cells inhibits the other and indirectly reinforces its own firing (the "sleep-wake flip-flop switch"). Such switches cause sharp transitions and avoid intermediate states of limbo. Hence, the system is stable in each end-state. This prevents, for instance, normal brains from entering REM during wakefulness.

Lu et al. [86], proposed that a similar type of mechanism could be the basis for the NREM-REM alternation: the "REM flip-flop switch". It is conceived as a subsidiary to the more general sleep-wake flip-flop switch described above. When the system is in REM-on mode, vlPAG and DpMe REM-off cells are inhibited, so that the REM expression can continue. When the system is in REM-off mode, SLD, vM and DGPi REM-on cells are inhibited and the system remains outside REM sleep (either in wake or NREM). Transitions between REM and NREM are thus a matter of seconds, with no intermediate state (it is either in NREM, REM, or wake mode), whereas it is thought that the underlying processes responsible for the alternation are slower.

The cholinergic and monoaminergic populations, which are the basis of the LCRIM, are considered here to have potential important modulatory roles, but they would not be part of the core REM sleep regulatory mechanism. Indeed, selective lesions of either the cholinergic or monoaminergic nuclei in the brainstem have shown relatively little effect on REM sleep [93–95]. These are arguments against the RI hypothesis described above.

Since a mutual inhibition mechanism alone would stabilize the system forever in the mode in which it is started, what causes the transitions? The most favored explanation takes its lead in the work by Franken [71], as described in the paragraph on short-term homeostasis. REM pressure is accrued during wake time and NREM sleep. REM sleep period timing is dictated by an underlying short-term homeostatic process. The daily amount of REM would be determined by a long-term process. One of the key points here is the nature and physiology of the REM pressure since it would ultimately determine the duration of the NREM-REM cycle (see further on).

5.4.3. The vlPAG GABA: gating of REM sleep and a close parallel to REM pressure

Using optogenetic manipulation and Caspase 3-mediated cell ablation, Weber at al. [97], confirmed that vlPAG GABAergic neurons powerfully suppress REM sleep. Activation of these neurons both greatly reduced NREM to REM transitions and shortened REM sleep maintenance. Optrode recording and calcium imaging showed that their activity was strongly suppressed at the onset of each REM sleep episode and increased abruptly at its termination, consistent with their functional role in gating REM sleep. The strong suppression of vlPAG activity during REM sleep could be mediated in part by inhibitory inputs from REM-on neurons. Indeed, REM-on GABAergic neurons in the pons, ventral and dorsal medulla, lateral hypothalamus, and preoptic area have all been shown to project to the vlPAG.

Cell-type-specific recording and calcium imaging were also performed [97] to characterize the spiking activity of these GABAergic neurons across sleep ultradian cycles. Shortening of REM episode duration by vlPAG GABA neurons by optogenetic manipulation led to a significant shortening of the subsequent inter-REM interval, likely due to a reduced dissipation of REM sleep pressure. Such a correlation suggests that the inter-REM interval is under homeostatic regulation, in which REM sleep pressure accumulated during inter-REM intervals is partially dissipated by each REM sleep episode.

Given the strong REM suppression effect of vlPAG GABAergic REM-off neurons, the slow decrease of their firing rates could gradually enhance the propensity of the next REM episode and thus regulate the ultradian timing of the REM/NREM alternation.

In sum, RI sees REM-on and REM-off neurons as sharing power in alternation through an exchange of excitatory and inhibitory signals. This dyad provides a functional REM oscillator. Issues are the relative rigidity of the model when intermittent awakenings interrupt the cycles and the minimal effect on REM sleep by lesions of cholinergic or monoaminergic nuclei in the brainstem.

MI sees rapid switches in and out of REM according to short- and long-term REM pressure. Issues include the nature and physiology of the REM pressure and the trigger for the alternation.

"REM-gating" vlPAG GABA neurons show a strong parallel between their firing and absence of REM behavior. Furthermore, the accumulation and dissipation of vlPAG GABAergic neuron activity across NREM/REM cycles parallels REM sleep pressure.

5.5. Number of cycles per night/24 h

The distribution of cycles during a night/24 h is a defining part of the analyzed subject. Studies have shown a Gaussian distribution of the number of cycles in mice [10] and rats [98]. Perhaps more astonishingly, the distribution is normal in humans, despite the far smaller number of cycles observed in a night (from 1 to 8, with a distribution mode of 4 or 5). This was demonstrated first in healthy controls studied at home [99], then in psychiatric patients [100]. Replication on a very large scale (2,312 nights), has recently been published [101]. In cell-type-specific ablation of GABAergic neurons, the amount of REM sleep increased significantly during both the light and dark phases, which was due primarily to an increased frequency of REM sleep episodes [97].

This normal distribution permits the use of parametrical analyses. One of the most interesting comparisons is between the number of cycles in a night/24 h and the ratio between the total durations of REM and NREM. If the correlation is close to zero, then having few or many cycles does not affect the total duration of either REM or NREM. This would support dependent relationships between REM and NREM, and hypotheses where REM replenishes vanishing NREM (ie, renewal). If the correlation is positive, more cycles will indicate a higher proportion of the total duration of REM sleep relative to NREM across the night/24 h. If the correlation is negative, more cycles will mean an increase in the proportion of NREM relative to REM during the night. The higher the relationship between the number of cycles and REM/NREM ratio, the stronger the independence between the sleep states. Since increases in the number of cycles generally have parallel increases in episode duration [86,91], this would fit preferentially with either REM- or NREM-centered hypotheses. The correlations between the number of cycles and the REM/NREM ratio have been clearly positive in each analyzed sample so far (rodents and humans).

Thus, when the proportion of REM over NREM duration is higher, there is a larger number of cycles and vice-versa. The positive correlations found in the different studies favor REM-centered

hypotheses on the alternation and differential regulations of NREM and REM sleep.

6. Energy Allocation (EA) and temperature

The idea that sleep's main purpose is the conservation of energy is outdated. Skepticism first arose when an 8 h metabolic rate reduction was estimated to be only about 10–15% more efficient than quiet wakefulness [102,103]. A behavior so highly conserved across species would appear to constitute an extravagant expenditure for the organism, considering the lost opportunities of foraging, mating, and increased risk of predation [2].

However, these calculations of energy savings were based only on metabolic rate reduction, which assumes all metabolic functions to be equally reduced during sleep. Yet, many biological operations are upregulated during sleep, such as macromolecule biosynthesis, intracellular transport, membrane repair, neural network reorganization, memory consolidation, immune function, and restorative processes. In his Energy Allocation hypothesis of sleep, Schmidt [13], postulates that state-dependent coupling of biological functions distributes energy resources in a manner that provides comparatively greater daily energy conservation than metabolic rate reduction. Sleep-wake cycling would downregulate specific biological processes in waking and upregulate them in sleep, thereby decreasing energy demands imposed by wakefulness and resulting in overall energy conservation. Computed this way, the actual energy savings from sleep may be more than 4-fold greater than previous estimates [104].

REM sleep-coupled functions, including memory consolidation, sensory-motor integration, visual system development and maintenance, and reproductive function, are energy-demanding. According to the present hypothesis, an energetic balance would be obtained in endotherms by temporarily suppressing thermoregulatory defenses. These defenses cease during REM sleep, even when the animal is sleeping in ambient temperatures well outside of the thermoneutral zone [105,106]. In consequence, the longer any single bout of REM, the more likely the CBT will deviate toward the ambient temperature. If the animal is to avoid spending excess energy to defend the core temperature, REM sleep bout durations are constrained by the animal's ability to retain heat, which is a function of its surface area to volume ratio [13]. Species with a smaller body mass (eg, rodents) indeed cycle much faster from one REM period to another and exhibit much shorter REM sleep bout durations compared to species with a larger body mass such as in man [107]. Cycling REM and NREM sleep could thus be an advantageous way for the organism to optimize total REM sleep quantity while minimizing the need for thermoregulatory defense [13].

Optimization of resource allocations at the whole organism level requires a top-down network control system capable of integrating key input variables such as energy status, thermoregulatory demands, and homeostatic sleep need. The ORX and Melanin-concentrating hormone (MCH) systems, through their diverse hypothalamic inputs and their extensive efferent projections, are ideal candidate structures for this role [108].

ORX neurons are almost entirely active during wake periods. ORX neurons increase the likelihood of transitions into wakefulness, whereas their inhibition increases the likelihood of transitions into sleep. Significant loss of ORX neurons leads to narcolepsy [109]. ORX neurons are also implicated in food-seeking, motivation, reward and addiction, autonomic, and neuroendocrine modulations [110].

MCH neurons are more active during sleep periods [111]. They increase the amount of time spent in SWS, and, even more so, in REM sleep. They are also involved in the regulation of feeding behavior, mood, and energy balance [112]. ORX neurons and MCH show reciprocal firing patterns and opposing effects on sleep states and diverse peripheral tissues [113].

Through the integration of thermoregulatory input, ORX and MCH appear to modulate the probability of behavioral state transitions from NREM sleep to either REM sleep or wakefulness. If the circumstances are not ideal for REM sleep, such as when ambient temperatures deviate from thermoneutrality and the organism must resort to thermoregulatory defenses such as shivering or brown adipose tissue thermogenesis, ORX would inhibit REM sleep by promoting arousal and heat production. However, if the ambient temperature is within thermoneutrality, the organism may forego thermoregulatory defense and, instead, opportunistically invest into REM sleep-coupled biological processes. The MCH system would be favored during warm thermoneutral ambient temperatures, particularly when energy balance is positive or during high sleep pressure. It would thus increase the probability of transitions from NREM to REM sleep, decrease the REM-to-REM sleep cycle length, and increase REM sleep bout durations [108].

Therefore, the Energy Allocation hypothesis proposes a comprehensive theory on the function of sleep. For what concerns REM and NREM alternation, the absence of thermoregulatory defenses during REM may explain why REM episode durations and the interval length between them is a function of species and their specific surface area to volume ratio.

7. Discussion

7.1. REM depends on NREM sleep to be expressed

Isolated NREM periods are commonly observed in polyphasic species and it appears that NREM does not need REM to be expressed. Things are different on the REM side. Although sleep begun by REM periods is described in infants and adult narcoleptic patients and is hence neurologically possible, the rule is that well-organized sleep begins with a NREM period. REM thus seems to be in some way harnessed to NREM sleep. Consequently, it is at least partially dependent on NREM.

7.2. A sleep-dependent process

There is consensus on the fact that the alternation is sleep-dependent. Theories proposing a sleep-independent general cycling phenomenon (BRAC, [56]), of which the NREM-REM alternation would be an example, have been confronted with two issues. First, interruptions by awakenings mostly push the cycles forward [59]. Second, REM sleep never starts the cycle after an awakening, as would be expected if the cycles were determined by a rigid internal clock [63].

7.3. Rebuttal of renewal-type theories

The concept that REM sleep's main function is to replenish vanishing NREM episodes was countered by two observations. No difference in attempts to enter REM sleep were observed after differential durations of NREM deprivation [77]. More successful attempts to enter REM were observed after longer durations of previous selective REM deprivation [71]. Some long-term REM pressure is thus accrued between sleep episodes (eg, daytime in humans), which is in direct contradiction to theories that consider the relationship between REM and NREM duration to be due exclusively to local exchanges [64]. The correlation found between the number of cycles per night/24 h and the REM/NREM ratio also supports distinct regulation mechanisms [99]. If we put the renewal-type theories aside, all remaining hypotheses consider

that both NREM and REM are under short- and long-term homeostasis, circadian, and allostatic influences.

7.4. Short-term homeostasis hypothesis

In the short-term homeostasis theory originally described by Vivaldi et al. [65], and later modified by Franken [71], the duration of a REM episode determines the duration of the interval to the subsequent REM episode in a negative-feedback loop mechanism. In the most referred-to short-term homeostasis version [71], REM pressure relies on two sources: long-term REM sleep homeostasis (for the daily amounts) and the short-term homeostasis accrued during the immediately preceding NREM episode (for the timing). The timing of the first REM episode is not explained in this theory.

The evidence in polyphasic animals was performed on preferential parts of the 24 h, sophisticated statistics were needed to deliver the results and the correlations were relatively weak [64,65]. Recent data confirmed them more clearly in mice [97]. Evidence in monophasic humans is however less compelling. One study used an extended sleep protocol to demonstrate such links [69]. In another study, in which both NREM and REM durations as well as SWA were measured [72], no preferential relationship emerged between REM and either the preceding or consecutive NREM interval.

7.5. NREM-centered hypotheses have lost traction

If each sleep state was cycling independently, we should expect random sleep patterns, which actually are the exception rather than the rule. It is presumably either NREM or REM that starts and maintains the cycling, with the other state adjusting to it.

Theories that put NREM at the helm of the cycling (eg, one-stimulus [78], REM by default [73]) propose that NREM cycles spontaneously and REM fills in below a certain SWA threshold. Although graphically appealing in SWA spectral power displays, no neurohormone or mediator has been found that parallels the cycling. Attempts to find a predictive model have been unsuccessful [71]. Ratios between REM and NREM duration and the number of cycles indicate a link between the latter and REM sleep, not NREM sleep [99,114,101].

7.6. REM-centered hypotheses

In the RI (LCRIM) hypothesis, two alternating groups of cells combine their action as a functional REM oscillator. REM-on cells inhibit and interrupt NREM and REM-off neurons end the REM episode. A limit is put to the maximal duration of a cycle, even if some elasticity ("E") has been later added.

This hypothesis is at odds with the short-term homeostasis theory: in the latter, the longer the REM period, the longer the latency to the next REM period. If a limit is set, as in the RI models, even with some elasticity ("E"), this latency should instead be shorter. Selective lesions of either the cholinergic or monoaminergic nuclei in the brainstem show relatively little effect on REM sleep [93–95]. These arguments plead for the cholinergic/aminergic theories to play a modulating influence rather than represent a central tenet of the alternation.

A MI was demonstrated between REM-on and REM-off cells. Both groups of cells tend to maintain their activity as long as nothing else intervenes [92,86,90]. This causes swift (flip-flop) switches between NREM and REM. Therefore, entry to and exit from REM activity is clear-cut, with no intermediate state of limbo. However, what causes the alternation is not obvious, since each state would tend to perpetuate itself ad infinitum. It is suggested (see Ref. [115]) that an underlying and fluctuating process based on REM pressure dictates the timing of REM sleep, as in the short-term homeostasis theory for REM sleep described earlier [71]. Alternately, the nature of REM pressure is still far from clear and it is still impossible to determine if it can modulate the excitability of cells to a timescale compatible with the REM cycles.

The gating from NREM to REM, and later from REM to either wake or NREM, has been shown to parallel the activity of vlPAG GABAergic neurons (fast synaptic inhibition during REM episode, rebound at its end). Also, the monitoring of ultradian cycles has shown a progressive decay of vlPAG firing during consecutive NREM sleep episodes, with a reset at each REM episode, the magnitude of which depended on the episode duration. A strong parallel is thus observed between the modulation of vlPAG GABAergic neuron activity and the accumulation and dissipation of REM sleep pressure [97]. It thus appears well suited for the ultradian regulation of the REM/NREM alternation.

What happens to NREM in a REM-centered hypothesis? In humans, SWA, which is considered a measure of NREM pressure, has been shown to be discharged in an exponentially negative way across the night. The combination of this progressively diminishing deep sleep homeostatic pressure and more or less regular interruptions by REM-on activity explains the usual pattern of NREM-REM cycling observed. It shows, for instance, why, when deep sleep is intense such as at the beginning of the night, REM may not succeed in interrupting it and may provide the typical patterns of skipped first REM, or only produce a short-duration REM episode. At the end of the night, diminishing NREM pressure and higher circadian influences may make REM periods longer and more frequent.

7.7. ORX and MCH, energy allocation and temperature

ORX and MCH neurons show reciprocal activity patterns, paralleling wake and sleep. More MCH firing is also paralleled by entry into REM sleep. These neurons are located in the Lateral Hypothalamus, a brain region dedicated to the integration of food-seeking, motivation, mood, reward and addiction, autonomic, and neuroendocrine modulations. State-dependent (Wake, NREM and REM) coupling of biological functions distributes energy resources in a manner that provides comparatively greater daily energy conservation than metabolic rate reduction.

As there is no thermoregulatory defense during REM sleep, endotherms are at risk of shifting toward ambient temperature. The duration of REM episodes would thus be limited by the species surface area to volume ratio. However, the theory does not explain the alternation by itself, since even at thermoneutral ambient temperature, REM sleep is eventually ended.

Perhaps thermosensitive REM sleep is an evolutionary remnant from ectotherm life (see Ref. [116]). Moreover, perhaps NREM and the cycling are ways to adapt this remnant to an endotherm world? Considering its omnipresence at birth and probably before it, perhaps REM is the first state in which our brains have functioned? Could it represent a link with our ontogeny and phylogeny?

7.8. NREM and REM pressures

NREM and REM "pressures" should still be considered today as virtual constructs that fit into theories to explain the potential to influence sleep into more NREM or more REM sleep at a given time. If we accept that NREM and REM are relatively independent from each other, then differential intensities of NREM and REM pressure should be present before sleep and eventually translate into more or less actual NREM and REM sleep in the 24 h or the night.

NREM pressure is reflected by the SWA, with the characteristic that more NREM pressure can partially be translated into a deeper

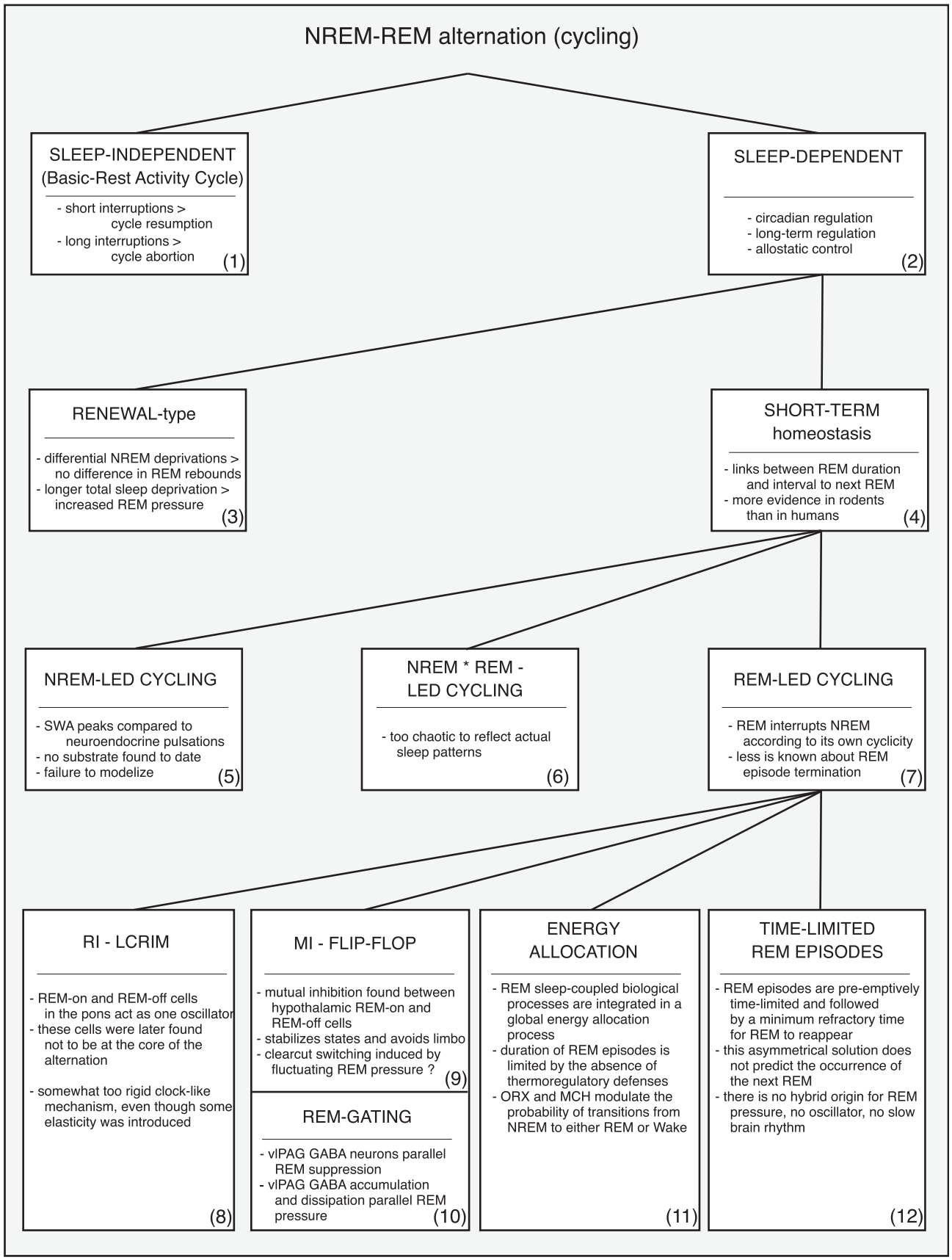

Fig. 1. (1) « > » stands for "gives rise to". Sleep-independent hypotheses are contradicted by these arguments; (2) in sleep-dependent hypotheses, duration and timing of cycles are influenced by long-term regulation, circadian regulation and allostatic control; (3) Renewal-type hypotheses are contradicted by these arguments; (5) NREM-LED cycling: NREM-centered hypotheses, where NREM leads the alternation; SWA: Slow Wave Activity; (6) NREM*REM-LED cycling: both REM and NREM would show a cyclicity of their own; (7) As in 5; 8. RI: Reciprocal Interaction, LCRIM: Limit-Cycle Reciprocal Interaction Model; (9) MI: Mutual Inhibition; (10) vlPAG: ventrolateral periaqueductal gray matter; (11) ORX: Orexin-hypocretin; MCH: Melatonin-Concentrating Hormone.

and shorter SWA. REM pressure can only be measured by the resistance to suppress attempts to enter REM and does not seem to show much flexibility - more REM pressure means more REM sleep duration.

Physiologically, some links have been established between REM pressure and localized cell groups.

REM deprivation in cats reduced the activity of REM-off cells, thus potentially facilitating transitions into REM sleep [117]. An increase in brain-derived neurotrophic factor (BDNF) has been associated with REM sleep deprivation [118]. Inhibition of vlPAG/DpMe GABAergic neurons after 6 h of REM deprivation was shown to block the expected rebound in REM sleep [91]. Most vlPAG GABAergic neurons are strongly suppressed at REM sleep onset and activated at its termination. Their activity decreases gradually between REM episodes and is reset by each REM episode in a duration-dependent manner, mirroring the accumulation and dissipation of REM sleep pressure [97].

7.9. Three metaphors for the distal end of REM episodes

What happens at the distal end of the cycles (also by definition the end of a NREM-REM cycle) remains something of a gray area. As a rule, the frontal end of the REM episode is preceded by NREM. The distal end may, to the contrary, be followed either by NREM (in the majority of cases in monophasic animals) or by wake (in the majority of polyphasic sleepers, sometimes rapidly followed by NREM). It is harder to find a common rule since there are two different endings.

I would consider three logical options: (1) REM pressure is interrupted by a conflicting NREM pressure and eventually yields power to it; (2) REM pressure fluctuates on its own basis, working underground and reappearing to interrupt NREM according to its own dynamics; (3): REM pressure launches a REM episode self-limited in time, with a refractory period following it, with no indication of when REM should return.

In the first case, the organization of NREM would be opposite that of REM: we should find NREM-on and NREM-off cells, as in a boxing metaphor. NREM-on would interrupt REM. However, no EEG (or other) signs have been described, showing that NREM is preparing to take power over REM (NREM attempting to disrupt REM sleep). Second, although sometimes confused, REM-off cells are not NREM-on cells, as suggested in concepts such as a sleep connectome ([119,91] comment by Le Bon on the electronic version). Third, the end of a REM period is not synonymous with entry into NREM, as we just saw above.

In the second case, REM surges and interrupts a passive NREM as in a sea snake metaphor. This is presently the most popular option (short-term homeostasis, Franken hypothesis, flip-flop model). Cycling relies on a supposedly fluctuating REM pressure and would represent a slow brain rhythm [115]. This concept is tempting when looking at human polysomnograms, but probably less so when observing those of polyphasic species, where isolated NREM periods are frequent and many REM periods are not immediately followed by NREM. The slow brain rhythm would also need to be quite different during daytime and nighttime in most animals.

Data are still insufficient to decide: (1) if what is accumulated during wake and NREM is of the same nature (Franken's version of the short-term homeostasis for instance); (2) whether REM pressure modulates neural excitability on a timescale that matches the mammalian sleep cycle.

In the third case, REM-on cells would inhibit REM-off cells, such as the vlPAG neurons. I propose that this would launch a REM episode limited in time, with REM-off neurons closing it after a duration pre-emptively determined by the species (not as a function of ambient temperature). There would be a minimum refractory time for REM to reappear. The REM pressure would not be cycling, only waiting for a new favorable opportunity to exert its action (a solid piece of NREM episode?), as in a hitch-hiking metaphor. This hypothesis would thus not predict when the next REM episode would happen. NREM would surge again, sooner or later, as a function of its own pressure. NREM would then either limit itself at that point and produce an isolated NREM period, as is frequently observed in polyphasic species, or it could be interrupted by a REM period, as a function of the local REM and NREM pressures. Each time, both NREM and REM pressures would be partially relieved while the system memorizes what is left over. More REM pressure would mostly be translated into more cycles rather than longer cycles [101]. This seems compatible with the progressive decay of vlPAG firing observed after the end of a REM episode [97]. Such an asymmetrical hypothesis would be quite flexible. It might explain why REM periods always seem limited in duration (periods longer than 20 min, for instance, are infrequent in humans). There would be no need for a hybrid origin of REM pressure, no oscillator and no slow brain rhythm.

7.10. Conclusions

As a general conclusion, after 65 years of research, the alternation of NREM and REM sleep is still a fascinating unsolved puzzle (see Fig. 1). The process is sleep-dependent. Both NREM and REM are under the influence of short-term and long-term homeostasis. They are also both under circadian and allostatic influences. Their regulation is thus relatively independent of each other. The renewal-type theories and cycles led by a fluctuating SWA have lost traction. REM-centered theories clearly are central. Reciprocal interaction theories face crucial questions. Mutual inhibition (Flip-flop) theories explain the swift changes observed between sleep states, but they rely on hypothetical REM pressure undulations. The comprehensive Energy Allocation theory explains why the absence of thermoregulatory defenses during REM sleep episodes limits their duration. The relationships between the ORX-MCH system in the LH and neurotransmitters GABA and glutamate need to be clarified. Links between the REM-inducing MCH and REM-inhibiting vlPAG GABA need to be uncovered. The nature of NREM and REM pressures still needs to be elucidated. Short-term homeostasis is the most popular theory underlying the cycling, although it still needs confirming evidence and may be overstated. Maybe an asymmetrical solution, with only a refractory period following REM episodes, could prove interesting. In that case, if there is a rhythm, it would not need to be a regular motion. And then it could be safer to speak of mere alternations that do not presuppose regularity.

Acknowledgments

I am extremely grateful to Roseanne Armitage and Tim King, for help with editing, and to Adrian Ocampo-Garcés, for critical and timely information.

Conflict of interest

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: https://doi.org/10.1016/j.sleep.2020.02.004.

References

[1] Aserinsky E, Kleitman N. Regularly occurring periods of eye motility, and concomitant phenomena, during sleep. Science 1953;118:273–4.

[2] Rechtschaffen A. Current perspectives on the function of sleep. Perspect Biol Med 1998;41:359–90.
[3] Krueger JM, Frank MG, Wisor JP, et al. Sleep function: toward elucidating an enigma. Sleep Med Rev 2016;28:46–54.
[4] Zepelin H. Mammalian sleep. In: Kryger MH, Roth T, Dement WC, editors. Principles and practice of sleep medicine. 3rd ed. Philadelphia, PA: Saunders; 2000. p. 2000.
[5] Elgar MA, Pagel MD, Harvey H. Sources of variation in mammalian sleep. Anim Behav 1990;5:991–5.
[6] Feinberg I, March JD, Fein G, et al. Period and amplitude analysis of 0.5-3 c/sec activity in NREM sleep of young adults. Electroencephalogr Clin Neurophysiol 1978;44:202–13.
[7] Borbély AA, Baumann F, Brandeis D, et al. Sleep deprivation: effect on sleep stages and EEG power density in man. Electroencephalogr Clin Neurophysiol 1981;51:483–95.
[8] Clément O, Sapin E, Bérod A, et al. Evidence that neurons of the sublaterodorsal tegmental nucleus triggering paradoxical (REM) sleep are glutamatergic. Sleep 2011;1(34):419–23.
[9] Diniz Behn CG, Ananthasubramaniam A, Booth V. Contrasting existence and robustness of REM/Non-REM cycling in physiologically based models of REM sleep regulatory networks. SIAM J Appl Dyn Syst 2013;12(12):279–314. 2013.
[10] Le Bon O, Popa D, Streel E, et al. Ultradian cycles in mice: definitions and links with REMS and NREMS. J Comp Physiol A Sens Neural Behav Physiol 2007;193:1021–32.
[11] Iber C, Ancoli-Israel S, Chesson A, et al., editors. The AASM manual for the scoring of sleep and associated events: rules, terminology, and technical specification. 1st ed. Westchester, IL: American Academy of Sleep Medicine; 2007.
[12] Rechtschaffen A, Kales A, editors. A manual of standardized terminology, techniques and scoring system of sleep stages in human subjects. Los Angeles: Brain Information Service/Brain Research Institute, University of California; 1968; 1968.
[13] Schmidt MH. The energy allocation function of sleep: a unifying theory of sleep, torpor, and continuous wakefulness. Neurosci Biobehav Rev 2014;47:122–53.
[14] Piéron H. Le problèÅme physiologique du sommeil. Paris: Masson; 1913.
[15] von Economo C. Sleep as a problem of localization. J Nerv Ment Dis 1930;71:249–59. 1930.
[16] Kronauer RE, Czeisler CA, Pilato SF, et al. Mathematical model of the human circadian system with two interacting oscillators. Am J Physiol 1982;242:R3–17.
[17] Borbély AA. A two process model of sleep regulation. Hum Neurobiol 1982;1:195–204.
[18] Daan S, Beersma DG, Borbély AA. Timing of human sleep: recovery process gated by a circadian pacemaker. Am J Physiol 1984;246:R161–83.
[19] Achermann P, Borbély AA. Simulation of human sleep: ultradian dynamics of electroencephalographic slow-wave activity. J Biol Rhythm 1990;5:141–57.
[20] Achermann P, Dijk DJ, Brunner DP, et al. A model of human sleep homeostasis based on EEG slow-wave activity: quantitative comparison of data and simulations. Brain Res Bull 1993;31:97–113.
[21] Massaquoi SG, McCarley RW. Extension of the Limit Cycle Reciprocal Interaction Model of REM cycle control. An integrated sleep control model. J Sleep Res 1992;1:138–43.
[22] Berger RJ, Oswald I. Effects of sleep deprivation on behaviour, subsequent sleep, and dreaming. J Ment Sci 1962;108:457–65.
[23] Williams HL, Hammack JT, Daly RL, et al. Responses to auditory stimulation, sleep loss and the eeg EEG stages of sleep. Electroencephalogr Clin Neurophysiol 1964;16:269–79.
[24] Moses JM, Johnson LC, Naitoh P, et al. Sleep stage deprivation and total sleep loss: effects on sleep behavior. Psychophysiology 1975;12:141–6.
[25] Webb WB, Agnew HW. Stage 4 sleep: influence of time course variables. Science 1971;174:1354–6.
[26] Carskadon MA, Dement WC. Effects of total sleep loss on sleep tendency. Percept Mot Skills 1979;48:495–506.
[27] Akerstedt T, Gillberg M. The circadian variation of experimentally displaced sleep. Sleep 1981;4:159–69.
[28] Dinges DF. Differential effects of prior wakefulness and circadian phase on nap sleep. Electroencephalogr Clin Neurophysiol 1986;64:224–7.
[29] Gillberg M, Akerstedt T. The dynamics of the first sleep cycle. Sleep 1991;14:147–54.
[30] Nakazawa Y, Kotorii M, Oshishima M, et al. Changes in sleep pattern after sleep deprivation. Folia Psychiatr Neurol Jpn 1978;32:85–93.
[31] Dement W, Greenberg S. Changes in total amount of stage four sleep as a function of partial sleep deprivation. Electroencephalogr Clin Neurophysiol 1966;20:523–6.
[32] Hartmann E, Baekeland F, Zwilling G, et al. Sleep need: how much sleep and what kind? Am J Psychiatr 1971;127:1001–8.
[33] Webb WB, Agnew HW. The effects of a chronic limitation of sleep length. Psychophysiology 1974;11:265–74.
[34] Dement W. The effect of dream deprivation. Science 1960;131:1705–7.
[35] Agnew HW, Webb WB, Williams RL. Comparison of stage four and 1-rem sleep deprivation. Percept Mot Skills 1967;24:851–8.
[36] Beersma DG, Dijk DJ, Blok CG, et al. REM sleep deprivation during 5 hours leads to an immediate REM sleep rebound and to suppression of non-REM sleep intensity. Electroencephalogr Clin Neurophysiol 1990;76:114–22.
[37] Whitehead WE, Robinson TM, Wincor MZ, et al. The accumulation of REM sleep need during sleep and wakefulness. Comm Behav Biol 1969;4:195–201.
[38] Feinberg I, Fein G, Floyd TC. EEG patterns during and following extended sleep in young adults. Electroencephalogr Clin Neurophysiol 1980;50:467–76.
[39] Gulevich G, Dement W, Johnson L. Psychiatric and EEG observations on a case of prolonged (264 hours) wakefulness. Arch Gen Psychiatr 1966;15:29–35.
[40] Kales A, Tan TL, Kollar EJ, et al. Sleep patterns following 205 hours of sleep deprivation. Psychosom Med 1970;32:189–200.
[41] Benoit O, Foret J, Bouard G, et al. Habitual sleep length and patterns of recovery sleep after 24 hour and 36 hour sleep deprivation. Electroencephalogr Clin Neurophysiol 1980;50:477–85.
[42] Le Bon O, Staner L, Hoffmann G, et al. The first-night effect may last more than one night. J Psychiatr Res 2001;35:165–72.
[43] Fröberg JE. Twenty-four-hour patterns in human performance, subjective and physiological variables and differences between morning and evening active subjects. Biol Psychol 1977;5:119–34.
[44] Akerstedt T, Froberg JE, Friberg Y, et al. Melatonin excretion, body temperature and subjective arousal during 64 hours of sleep deprivation. Psychoneuroendocrinology 1979;4:219–25.
[45] Blake MJF. Time of day effects on performance in a range of tasks. Psychonomic Sci 1967;9:349–50.
[46] Colquhoun WP. Circadian variations in mental efficiency. Biological rhythms and human performances. London: Academic; 1969. p. 39–107.
[47] Mills JN, Minors DS, Waterhouse JM. The effect of sleep upon human circadian rhythms. Chronobiologia 1978;5:14–27.
[48] Zulley J, Wever R, Aschoff J. The dependence of onset and duration of sleep on the circadian rhythm of rectal temperature. Pflügers Archiv 1981;391:314–8.
[49] Kleitman N. Sleep and wakefulness as alternating phases in the cycle of existence. Chicago: University of Chicago Press; 1939.
[50] Aschoff J, Wever R. Human circadian rhythms: a multioscillatory system. Fed Proc 1976;35. 236-232.
[51] Czeisler CA, Duffy JF, Shanahan TL, et al. Stability, precision, and near-24-hour period of the human circadian pacemaker. Science 1999;284:2177–81.
[52] Weitzman ED, Nogeire C, Perlow M, et al. Effects of a prolonged 3-hour sleep-wake cycle on sleep stages, plasma cortisol, growth hormone and body temperature in man. J Clin Endocrinol Metab 1974;38:1018–30.
[53] Carskadon MA, Dement WC. Sleepiness and sleep state on a 90-min schedule. Psychophysiology 1977;14:127–33.
[54] McEwen BS, Stellar E. Stress and the individual. Mechanisms leading to disease. Arch Intern Med 1993;153:2093–101.
[55] Chen X, Redline S, Shields AE, et al. Associations of allostatic load with sleep apnea, insomnia, short sleep duration, and other sleep disturbances: findings from the National Health and Nutrition Examination Survey 2005 to 2008. Ann Epidemiol 2014;24:612–9.
[56] Kleitman N. The nature of dreaming. In Wolstenholme GEW. In: O'Connor M, editor. The nature of sleep. Churchill, London; 1961. p. 1961.
[57] Kleitman N. Basic rest-activity cycle - 22 years later. Sleep 1982;5:311–7.
[58] Globus GG. Rapid eye movement cycle in real time. Implications for a theory of the D-state. Arch Gen Psychiatr 1966;15:654–9.
[59] Gaillard JM, Tuglular I. The orthodox-paradoxical sleep cycle in the rat. Experientia 1976;32:718–9.
[60] Brezinova V. Sleep cycle content and sleep cycle duration. Electroencephalogr Clin Neurophysiol 1974;36:275–82.
[61] Miyasita A, Fukuda K, Inugami M. Effects of sleep interruption on REM-NREM cycle in nocturnal human sleep. Electroencephalogr Clin Neurophysiol 1989;73:107–16.
[62] Grözinger M, Beersma DGM, Fell J, et al. Is the nonREM-REM sleep cycle reset by forced awakenings from REM sleep? Physiol Behav 2002;77:341–7.
[63] Feinberg I, Floyd TC. Systematic trends across the night in human sleep cycles. Psychophysiology 1979;16:283–91.
[64] Benington JH, Heller HC. REM-sleep timing is controlled homeostatically by accumulation of REM-sleep propensity in non-REM sleep. Am J Physiol 1994;266:R1992–2000.
[65] Vivaldi EA, Ocampo A, Wyneken U, et al. Short-term homeostasis of active sleep and the architecture of sleep in the rat. J Neurophysiol 1994;72:1745–55.
[66] Ursin R. Sleep stage relations within the sleep cycles of the cat. Brain Res 1970;20:91–7.
[67] Weitzman ED, Kripke DF, Pollak C, et al. Cyclic activity in sleep of macaca mulatta. Arch Neurol 1965;12:463–7.
[68] Kripke DF, Crowley TJ, Pegram GV, et al. Circadian rhythmic amplitude modulation of Berger-region frequencies in electroencephalograms from Macaca mulatta. Rassegna Neurol Vegetativa 1968;22:519–25.
[69] Barbato G, Wehr TA. Homeostatic regulation of REM sleep in humans during extended sleep. Sleep 1998;21:267–76.
[70] Hartmann E. Mechanism underlying the sleep-dream cycle. Nature 1966;212:648–50.
[71] Franken P. Long-term vs. short-term processes regulating REM sleep. J Sleep Res 2002;11:17–28.
[72] Le Bon O, Linkowski P. Absence of systematic relationships between REMS duration episodes and spectral power Delta and Ultra-Slow bands in contiguous NREMS episodes in healthy humans. J Neurophysiol 2013;110:162–9.
[73] Horne JA. REM sleep - by default? Neurosci Biobehav Rev 2000;24:777–97.

[74] Kales A, Hoedemaker FS, Jacobson A, et al. Dream deprivation: an experimental reappraisal. Nature 1964;204:1337–8.
[75] Endo T, Roth C, Landolt HP, et al. Selective REM sleep deprivation in humans: effects on sleep and sleep EEG. Am J Physiol 1998;274:R1186–94.
[76] Cox DR. Renewal theory. London: Methuen; 1962.
[77] Ocampo-Garcés A, Molina E, RodriÆguez A, et al. Homeostasis of REM sleep after total and selective sleep deprivation in the rat. J Neurophysiol 2000;84:2699–702.
[78] Feinberg I, March JD. Cyclic delta peaks during sleep: result of a pulsatile endocrine process? Arch Gen Psychiatr 1988;45:1141–2.
[79] Preud'homme XA, Lanquart JP, Mendlewicz J, et al. Distribution of delta activity across nonrapid eye movement sleep episodes in healthy young men. Sleep 1997;20:313–20.
[80] Feinberg I, March JD. Observations on delta homeostasis, the one-stimulus model of NREM-REM alternation and the neurobiologic implications of experimental dream studies. Behav Brain Res 1995;69:97–108.
[81] Preud'homme XA, Lanquart J-P, Krystal AD, et al. Modeling slow-wave activity dynamics: does an exponentially dampened periodic function really fit a single night of normal human sleep? Clin Neurophysiol 2008;119:2753–61.
[82] Hobson JA, McCarley RW, Wyzinski PW. Sleep cycle oscillation: reciprocal discharge by two brainstem neuronal groups. Science 1975;189:55–8.
[83] McCarley RW, Hobson JA. Neuronal excitability modulation over the sleep cycle: a structural and mathematical model. Science 1975;189:58–60.
[84] Steriade M, McCarley RW. Brainstem control of wakefulness and sleep. New York: Plenum Press; 1990.
[85] McCarley RW, Massaquoi SG. A limit cycle mathematical model of the REM sleep oscillator system. Am J Physiol 1986;251:R1011–29.
[86] Lu J, Sherman D, Devor M, et al. A putative flip-flop switch for control of REM sleep. Nature 2006;441:589–94.
[87] Boissard R, Gervasoni D, Schmidt MH, et al. The rat ponto-medullary network responsible for paradoxical sleep onset and maintenance: a combined microinjection and functional neuroanatomical study. Eur J Neurosci 2002;16:1959–73.
[88] Sakai K, Crochet S, Onoe H. Pontine structures and mechanisms involved in the generation of paradoxical (REM) sleep. Arch Ital Biol 2001;139:93–107.
[89] Onoe H, Sakai K. Kainate receptors: a novel mechanism in paradoxical (REM) sleep generation. Neuroreport 1995;6:353–6.
[90] Weber F, Chung S, Beier KT, et al. Control of REM sleep by ventral medulla GABAergic neurons. Nature 2015;526:435–8.
[91] Hayashi Y, Kashiwagi M, Yasuda K, et al. Cells of a common developmental origin regulate REM/non-REM sleep and wakefulness in mice. Science 2015;350:957–61.
[92] Saper CB, Chou TC, Scammell TE. The sleep switch: hypothalamic control of sleep and wakefulness. Trends Neurosci 2001;24:726–31.
[93] Jones BE, Harper ST, Halaris AE. Effects of locus coeruleus lesions upon cerebral monoamine content, sleep-wakefulness states and the response to amphetamine in the cat. Brain Res 1977;124:473–96.
[94] Mouret J, Coindet J. Polygraphic evidence against a critical role of the raphe nuclei in sleep in the rat. Brain Res 1980;186:273–87.
[95] Shouse MN, Siegel JM. Pontine regulation of REM sleep components in cats: integrity of the pedunculopontine tegmentum (PPT) is important for phasic events but unnecessary for atonia during REM sleep. Brain Res 1992;571:50–63.
[97] Weber F, Hoang Do JP, Chung S, et al. Regulation of REM and non-REM sleep by periaqueductal GABAergic neurons. Nat Commun 2018 Jan 24;9(1):354. 2018.
[98] Le Bon O, Ocampo-Garces A, Neu D, et al. Links between the number of sleep ultradian cycles and REMS duration: confirmation in rats. Neurophysiol Clin 2009a;39:133–4.
[99] Le Bon O, Staner L, Rivelli SK, et al. Correlations using the NREM-REM sleep cycle frequency support distinct regulation mechanisms for REM and NREM sleep. J Appl Physiol 2002;93:141–6.
[100] Le Bon O, Hoffmann R, Staner L, et al. Relationships between the number of ultradian cycles and key sleep variables in outpatients with major depressive disorder. Psychiatr Res 2009b;165:60–7.
[101] Le Bon O, Lanquart JP, Hein M, et al. Sleep ultradian cycling: statistical distribution and links with other sleep variables, depression, insomnia and sleepiness - a retrospective study on 2,312 polysomnograms. Psychiatr Res 2019;279:140–7. https://doi.org/10.1016/j.psychres.2018.12.141.
[102] Brebbia DR, Altshuler KZ. Oxygen consumption rate and electroencephalographic stage of sleep. Science 1965 Dec 17;150(3703):1621–3. 1965.
[103] Zepelin H. Mammalian sleep. In: Kryger MH, Roth T, Dement WC, editors. Principles and practice of sleep medicine. 1st ed. Philadelphia: W.B. Saunders Co.; 1989. p. 1989.
[104] Schmidt MH, Swang TW, Hamilton IM, et al. State-dependent metabolic partitioning and energy conservation: a theoretical framework for understanding the function of sleep. PLoS One 2017;12(10):e0185746. 2017.
[105] Hendricks JC. Absence of shivering in the cat during paradoxical sleep without atonia. Exp Neurol 1982 Mar;75(3):700–10. 1982.
[106] Parmeggiani PL. Thermoregulation and sleep. Front Biosci 2003 May 1;8:s557–67. 2003.
[107] Zepelin H, Siegel J, Tobler I. Mammalian sleep. In: Kryger MH, Roth T, Dement WC, editors. Principles and practice of sleep medicine. 4th ed. Philadelphia: Elsevier Saunders; 2005. p. 91–100.
[108] Latifi B, Adamantidis A, Bassetti C, et al. Sleep-wake cycling and energy conservation: role of hypocretin and the lateral hypothalamus in dynamic state-dependent resource optimization. Front Neurol 2018 Oct 5;9:790. https://doi.org/10.3389/fneur.2018.00790. eCollection 2018.
[109] Mignot E, Lammers GJ, Ripley B, et al. The role of cerebrospinal fluid hypocretin measurement in the diagnosis of narcolepsy and other hypersomnias. Arch Neurol 2002;59:1553–62. 2002.
[110] Sutcliffe JG, de Lecea L, October. The hypocretins: excitatory neuromodulatory peptides for multiple homeostatic systems, including sleep and feeding. J Neurosci Res 2000;62(2):161–8. 2000.
[111] Peyron C, Sapin E, Leger L, et al. Role of the melaninconcentrating hormone neuropeptide in sleep regulation. Peptides 2009;30(11):2052–9. 2009.
[112] Verret L, Goutagny R, Fort P, et al. A role of melanin-concentrating hormone producing neurons in the central regulation of paradoxical sleep. BMC Neurosci 2003;9(4):19.
[113] Hassani OK, Lee MG, Jones BE. Melanin-concentrating hormone neurons discharge in a reciprocal manner to orexin neurons across the sleep-wake cycle. Proc Natl Acad Sci Unit States Am 2009;106:2418–22. https://doi.org/10.1073/pnas.0811400106.
[114] Le Bon O, Chabanski S, Dramaix M, et al. Inverse association between Slow Wave Activity per cycle and the number of ultradian sleep cycles per night in healthy humans. Clin Neurophysiol 2005;116:1493–500.
[115] Weber F. Modeling the mammalian sleep cycle. Curr Opin Neurobiol 2017;46:68–75.
[116] Nicolau MC1, Akaàrir M, Gamundí A, et al. Why we sleep: the evolutionary pathway to the mammalian sleep. Prog Neurobiol 2000 Nov;62(4):379–406. 2000.
[117] Mallick BN, Siegel JM, Fahringer H. Changes in pontine unit activity with REM sleep deprivation. Brain Res 1990;515:94–8.
[118] Datta S, Knapp CM, Koul-Tiwari R, et al. The homeostatic regulation of REM sleep: a role for localized expression of brain-derived neurotrophic factor in the brainstem. Behav Brain Res 2015;292:381–92.
[119] Vyazovskiy VV. Mapping the birth of the sleep connectome. Science 2015;350:6263.