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Review

Epilepsy: The path to a novel concept of sleep neurology

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ABSTRACT

This brief review aims at enhancing the understanding on the concepts of sleep neurology among neurologists. Because some epileptic disorders exhibit significant wake/sleep dependency, the present manuscript focuses on the effects of sleep on epilepsy. The basic knowledge of sleep is briefly reviewed with special reference to epilepsy. In this review, emphasis is laid on a unique phenomenon, which exhibits significant changes in motor phenomenon in accordance with state changes - response-reversal. In addition, as a clinically applicable index to suggest brain chemical balances, atonia during non-rapid eye movement sleep is also introduced. Finally, the importance of the recognition of sleep health is emphasized. Epilepsy is concluded to be a useful disease condition to study the area of sleep neurology. Sleep neurology must be a fascinating research area for many neurologists researching epilepsy.

KEYWORDS: response reversal, atonia, sleep health

INTRODUCTION

A major interest in the field of neurology has focused on neurological symptoms during wakefulness, and very few neurologists paid much attention to symptoms during sleep or alterations of symptoms due to state changes. However, individuals sleep for approximately 1/4-1/3 of their lifetime. Neurological systems are acting among every state, and studies on their disturbances in each state are indispensable for a better understanding of neurological systems.

Certain epileptic disorders exhibit significant wake/sleep dependency. Therefore, the study of epilepsy could lead to a greater understanding of neuronal activity during sleep. This brief review is expected to provide a greater recognition of neurological activity during sleep.

Effects of sleep on epilepsy

1. Effects of states

By summarizing previous results, Shouse *et al.* [1] showed that neural generators of synchronous electroencephalography (EEG) oscillations combine to promote electrographic seizure propagation during non-rapid eye movement (NREM) sleep and drowsiness, and antigravity muscle tone permits seizure-related movement. In addition, the same review [1] described that neural generators of asynchronous neuronal discharge patterns reduce electrographic seizures during alert waking and rapid eye movement (REM) sleep, and skeletal motor paralysis blocks seizure-related movement during REM sleep.

According to Gowers [2], 21% of institutionalized patients exhibit seizures during sleep, 42% during the awake state, and 37% during wake and sleep states. In contrast, according to Janz [3], 45% of non-institutionalized patients exhibit generalized tonic-clonic seizures during sleep, 34% during the awake state, and 21% during wake and sleep states.

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Méndez and Radtke [4] summarized the effects of sleep states on epilepsy as follows. 1) Awakening epilepsies are primary generalized seizure disorders, which include juvenile myoclonic epilepsy, childhood- and juvenile-absence epilepsies, and generalized tonic-clonic seizures, upon awakening. These seizures are more prominent during the first two hours after awakening. 2) Partial seizures with secondary generalization are regarded as sleep epilepsies, as well as other partial seizure disorders that exhibit centrotemporal spikes and the Landau-Kleffner syndrome. Despite increased epileptic abnormalities during NREM sleep in patients with West syndrome (WS), there is a marked decrease in the frequency of clinical spasms not only during REM sleep but also during NREM sleep. Clinical seizures of this syndrome are most likely to occur prior to sleep or upon awakening. Patients with Lennox-Gastaut syndrome (LGS) exhibit diffuse seizures throughout the sleep/wake cycle. However, tonic seizures of this syndrome are continuously facilitated by sleep. Epilepsy with continuous spike-and-wave forms or electrical status epilepticus during slow-wave sleep are diagnosed according to EEG findings during slow-wave sleep stages. Seizures in patients with Panayiotopoulos syndrome (infantile variant of benign childhood epilepsy with occipital paroxysms) occur more often during sleep (70%) than wakefulness (17%) or upon awakening (13%) [5]. Recently, Awad and Lüders [6] proposed a concept of hypnopompic seizures, whose only manifestation is characterized by arousal from sleep.

In contrast to adults with inter-ictal epileptiform discharges (IEDs) that are activated by stages 3 and 4 of NREM sleep [7], IEDs in children are more prevalent during stage 1 and 2 sleep [8]. Focal IEDs that occur during REM sleep are reported to be more accurate for seizure localization compared with other sleep states [9]. The term "epileptic components of NREM (stages 3 & 4) and antiepileptic components of REM sleep" was used by Shouse et al. [1] and also shown by Minecan *et al.* [10] (Figure 1).

2. Effects of sleep quantity and quality

The loss of sleep or sleep-wakefulness rhythm irregularities have been reported to contribute to the production or precipitation of seizures in some individuals [11], including patients with epilepsy. Seizures can disturb sleep, and sleep disruption can interfere with seizure control [12].

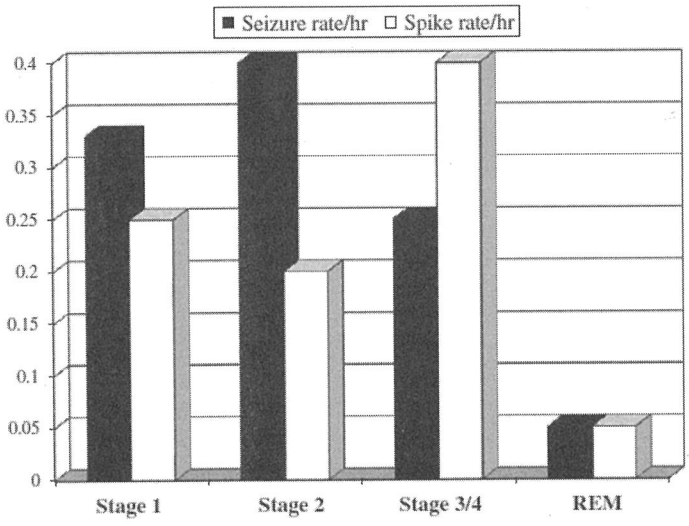

Figure 1. Seizure and spike rate/hour during various sleep stages. This figure is cited from manuscript by Kothare, S. V. and Kaleyias, J. 2010, Sleep Med., 11, 674. Reprinted with permission from Elsevier. This figure was made based on results from Minecan *et al.* [10].

Sleep debt

Sleep deprivation has been shown to increase the chance of detecting IEDs during EEG recordings [13, 14] (Gibbs and Gibbs 1947; Fountain *et al.* 1998). In addition, sleep deprivation is suggested to involve specific epileptogenic stress in some individuals [11]. In a retrospective study comparing routine sleep EEG and subsequent sleep-deprived EEG with sleep, a 52% activation rate of IEDs was observed in the latter group, independent of sleep duration [14] (Fountain *et al.* 1998). Subsequently, sleep deprivation became established as an activating method for eliciting epileptiform activity while performing EEGs [15]. However, the exact mechanisms of sleep deprivation activation of seizures remain to be shown, although the roles of gamma-aminobutyric acid (GABA), adenosine, melatonin, and orexin have been proposed [8]. According to Matos *et al.* [16], the effect of sleep deprivation on seizure occurrence was shown to vary among each epilepsy syndrome. Sleep deprivation was shown to trigger primarily generalized seizures, especially in younger individuals, as well as juvenile myoclonic epilepsy and idiopathic generalized seizures, in contrast to partial seizures. The study of the effects of sleep deprivation on epilepsy is thought to provide insight into effective clinical intervention [17]. It is important to note that studies that compared sleep-deprived EEG with drug-induced sleep EEG have reported conflicting findings [15].

The sleep-wakefulness rhythm

Disturbances in the sleep-wakefulness rhythm have been reported in child patients with intractable epilepsy [18, 19]. In amygdala-kindled rats, a single, full-blown seizure can alter the architecture of sleep-wakefulness cycles [20]. In addition, the susceptibility of seizures to circadian modulation has been previously reviewed [21].

The author examined the chronological alteration of the sleep-wakefulness rhythm in patients with WS and LGS [22], assuming that both syndromes might share the common underlying neurological abnormality. This assumption arose from the observation that some WS patients became LGS patients [23]. Both syndromes represent catastrophic types of epilepsy observed in young children [24]. Patients were assigned to benign or intractable groups according to seizure prognosis [22]. Disturbances in sleep-wakefulness rhythms in the benign patient group were indistinguishable from age-matched controls (age-matched patients with epilepsies other than WS or LGS), although these results were only observed at 2-4 years after cessation of epileptic seizures. In contrast, sleep-wakefulness rhythms of patients in the intractable group were different from controls during the observation period. Intractable seizures were likely to prevent sleep-wakefulness rhythm from normalization. Disturbances in sleep-wakefulness rhythm are likely to be more severe in patients with WS and LGS than in child patients with other types of epilepsy. It should also be noted that disturbances of sleep-wakefulness rhythm were more severe in the intractable group. Underlying neuronal mechanisms that disrupt sleep-wakefulness rhythm might be involved in the pathophysiology of WS and LGS.

Nocturnal insomnia and excessive daytime sleepiness are often reported in patients with epilepsy [25, 26]. Kothare and Kaleyias [8] summarized several factors that produce sleep disruption, including disturbance of sleep-wakefulness rhythms in child patients with epilepsy. It is thought that this could also hold true for adult patients (Figure 2).

Sleep physiology

In the former session, the effects of sleep on epilepsy have been briefly reviewed. However, the neuronal mechanisms involved in the production of these state-dependent alterations of seizures and IEDs remain poorly understood. The pathophysiology of epilepsy syndrome exhibiting state-dependency is thought to be involved in sleep mechanisms, and the following section will address the current knowledge of sleep mechanisms.

Sleep stages can be determined by EEG, electro-occulogram, and electromyogram (EMG) [27]. Rapid eye movements can be observed during wakefulness and REM sleep, as well as high-voltage EEG during stages 3 and 4, high EMG levels during wakefulness and stage 1, and low EMG levels during REM sleep. In terms of sleep stages during the night, deep NREM sleep stage is

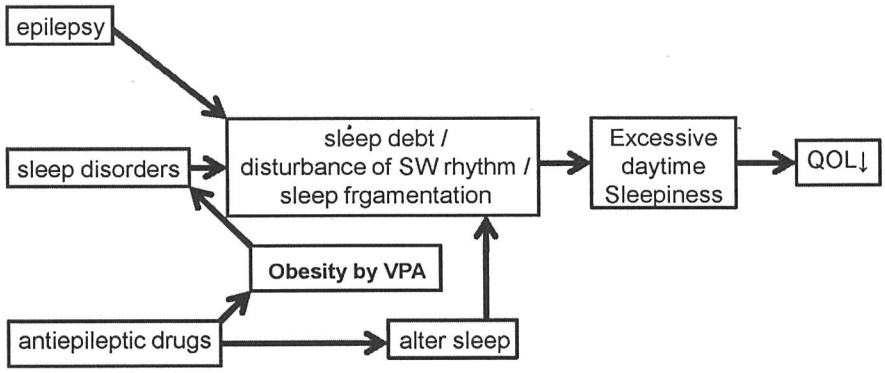

Figure 2. Etiology of sleep disruption in epilepsy patients. Modified figure 2 of manuscript by Kothare, S. V. and Kaleyias, J. 2010, Sleep Med., 11, 674. Reprinted with permission from Elsevier. SW: sleep-wakefulness; QOL: quality of life; VPA: valproate acid.

most prevalent during the beginning of the night; as night progresses, proportionally more and more time is spent in REM sleep, with approximately 90 minutes of the NREM-REM cycle. In addition, the NREM-REM sleep period alternates between 50- to 60-minute sleep cycles during the neonatal period, 75 minutes in 2-year-olds, and 84 minutes in 5-year-olds, respectively [28].

1. Sleep/wake centers

Results from pathological examinations of the 1920s proposed the concept of a sleep center, as well as a wake center [29], and recent advancements in neuroscience have led to a better understanding of the anatomical, pharmacological, and physiological details of these centers. Because both centers inhibit each other, activation of one of the centers results in continuous activation [30]. This model could explain the continuity of states, but fails to explain state changes. In addition, this model does not explain the alterations between NREM and REM sleep stages.

2. Brain activities during sleep

Table 1 summarizes results from studies on brain activities during sleep [31-33]. During REM sleep, activation of the pontine tegmentum, amygdala, and secondary optic area has been detected. Cholinergic neurons at the mesopontine junction, such as the pedunculopontine tegmental nucleus and laterodorsal tegmental nucleus, are thought to be involved in cortical activation and muscle atonia during REM sleep, and the sublaterodorsal tegmental nucleus has recently been shown to be involved in the onset of REM sleep [34]. In contrast to the NREM sleep stage, the REM sleep stage is characterized by muscle atonia due to hyperpolarization of motoneurons and cortical activation. These phenomena are the underlying neuronal mechanisms that produce the epileptic components of NREM sleep stages and the antiepileptic components of REM sleep [1].

3. Response-reversal

Response-reversal is a unique phenomenon that exhibits remarkable alterations of motor phenomena with stage switches. The recognition of this phenomenon is believed to be essential for the understanding of sleep neurology.

Stimulation of the pontomesencephalic reticular formation results in two distinct changes in masseteric reflex excitability, which are dependent on the behavioral state of the animal. During wakefulness and quiet sleep (animal state nearly equal to NREM sleep in humans), reticular stimulation has been shown to result in increased reflex excitability. However, during active sleep (animal state nearly equal to REM sleep in humans), identical stimulus delivered to the same reticular site leads to profound reflex suppression, and this phenomenon is termed response-reversal [35, 36] (Figure 3). Amplitude of the brainstem masseteric (jaw closing) reflex (mososynaptic reflex), which is continuously induced in freely moving, adult cats, serves as a baseline control for

Table 1. PET studies on brain activities during sleep.

	Light NREM	Deep NREM	REM
Maquet *et al.*, 1997		↓: pons, midbrain, basal brain, orbito-prefrontal Cx	↑: pontine tegmentum, lt thalamus, amygdale, ant. cingulated gyrus ↓: post. cingulate gyrus, frontal association Cx
Braun *et al.*, 1997		↓: brainstem, thalamus, basal forebrain, frontal/parietal association Cx	↑: secondary optic area ↓: frontal association Cx
Kajimura *et al.*, 1999	↓: pons, cerebellum, thalamus, putamen, ant. cingulate gyrus	↓: portions during light NREM + midbrain, hypothalamus, basal forebrain, caudate, post.cingulate gyrus	
Summary		↓: pons, thalamus, basal forebrain, association Cx	↑: pontine tegmentum, amygdale, secondary optic area ↓: association Cx

Cx: Cortex

analysis of reflex modulation. At randomly spaced intervals, high-frequency stimulation is applied to the ponto-mesencephalic reticular formation for 4-sec periods. During states of wakefulness and quiet sleep, amplitude of the masseteric reflex significantly increases during superimposed reticular stimulation. When the animal enters active sleep, however, reticular stimulation (using identical parameters for stimulation) results in significantly decreased reflex amplitude.

Response-reversal could be mimicked by chemical agents. One of the examples was shown in Figure 4 [37]. This report shows two types of temporal inhibition of medullary-induced neck muscle tone suppression. This inhibition is elicited by pontine lidocaine injection, which temporally reduces membrane excitability. Long-train stimulation (200-ms trains of 0.2-ms pulses at 100 Hz) was delivered to the medullary inhibitory area (shown in B) at the closed arrowheads in the upper panel. The average waveforms of rectified EMG changes induced by short-train stimulation (6.3-ms trains of three 0.2-ms pulses at 330 Hz, open arrowheads) are shown in the lower panel. Constant stimulus intensity (40 μA) was used during each trial. Upon pre-injection stimulation, both long and short trains resulted in bilateral suppression of neck muscle tone. After lidocaine was injected into sites shown in A, long trains failed to reduce muscle activity at 5, 10, 11, and 20 minutes after lidocaine injection. In addition, long trains elicited excitation, and short trains contained muscle facilitation (arrows) prior to attenuated suppression. Short trains resulted in reduced muscle tone, although to a lesser degree of suppression compared with waveforms obtained prior to lidocaine injection. At 45 and 46 minutes after lidocaine injection, both long and short trains resulted in bilateral suppression of neck muscle tone, again. This study demonstrated that identical stimulation delivered to the medurally reticular formation resulted in different effects, and response-reversal might be mimicked by lidocaine injection.

Another example of chemically mimicked response-reversal was shown in Figure 5 [38]. This study showed suppression of the Ia-monosynaptic reflex following bicuculline

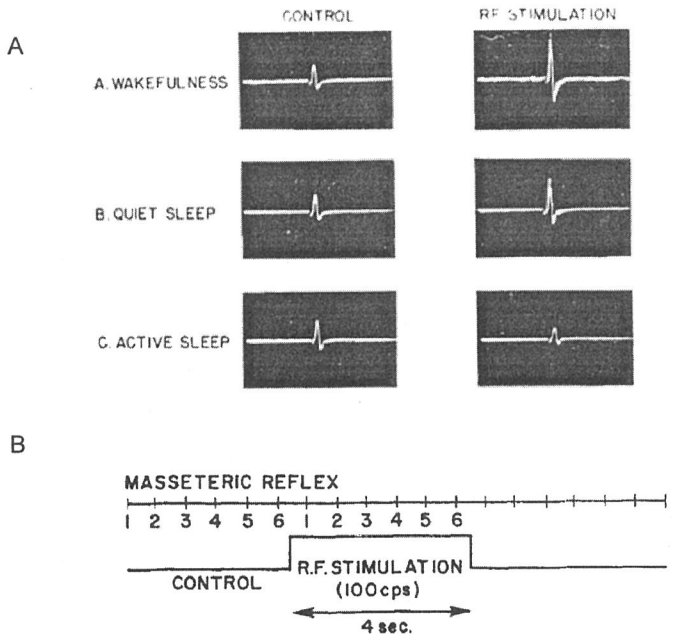

Figure 3. An example of response-reversal. A represents Fig. 2 in the manuscript by Chase, *et al.* 1976, Exp. Neurol., 50, 561, and B represents Fig. 1 in the same paper. Reprinted with permission from Elsevier.

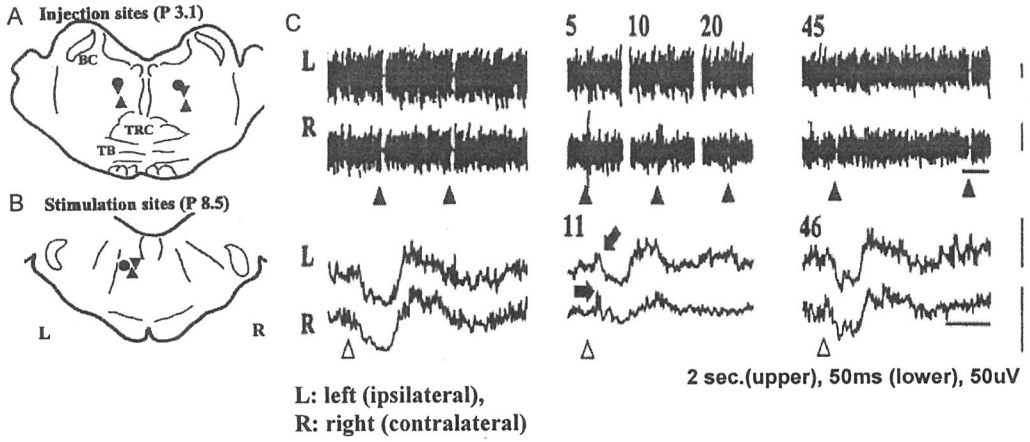

Figure 4. Temporal inhibition of medullary-induced neck muscle tone suppression elicited by a pontine lidocaine injection. A and B represent Fig. 1 in the manuscript by Kohyama, *et al.* [37] and C is from Fig. 2 in the same paper with permission.

(GABA A antagonist) injection into the nucleus pontis oralis. A shows anatomical location of effective injections site in the nucleus pontis oralis, and B shows examples of individual reflexes, which were elicited by electrical stimulation of the dorsal root at the 7th lumbar segment prior to (B1) and after bicuculline injection. Reflex amplitude was reduced following bicuculline administration (B2), and response-reversal was thought to be mimicked by bicuculline injection.

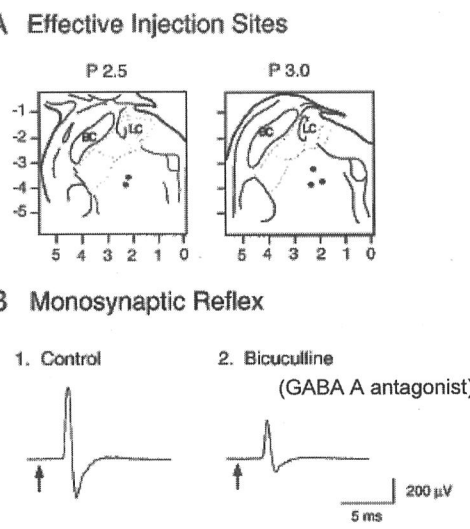

Figure 5. Response-reversal mimicked by modulation of chemical agents (Fig. 1 in manuscript by Xi, M. C., Morales, F. R., and Chase, M. H. 2001, J. Neurophysiol., 86, 1908, with permission from Am. Physiol. Soc.).

A schematic drawing of a parasagittal brainstem section was shown in Figure 6-A [39]. As shown in B and C of this Figure, activities of intrinsic chemical substances are significantly altered between states, which result in altered functional connections within the central nervous system. For example, release of GABAergic inhibition seems to be required for the activation of the pedunculopontine tegmental nucleus to activate the inhibitory system during REM sleep. Activity of each system (excitatory/inhibitory/locomotor) is modified by states (balance between intrinsic chemical substances), and altered activities of intrinsic chemical substances are likely to be responsible for underlying neuronal mechanisms that produce response-reversal.

4. Atonia during NREM sleep

A simple index that reflects the balance between monoaminergic and cholinergic activity in the brainstem has been introduced. Muscle tone is diminished during REM sleep, whereas muscle tone is likely preserved during NREM sleep. However, the NREM sleep stage is often experienced in conjunction with diminished chin muscle activity (Figure 7). Petre-Quadens [40] reported that the percentage of chin muscle atonia during NREM sleep (% ATNR) in ten normal children aged less than 5 years old was 14.7%. In addition, 9.0% ATNR was observed in four normal children aged five to fifteen years, 2.4% in individuals aged fifteen to twenty-five years, and 0.9% in a 62-year-old individual. According to Werth *et al.* [41], chin muscle atonia during NREM sleep appears at a constant rate of 10-15% throughout the night in healthy, young adults. Our study [42] determined that the average % ATNR in 25 children aged 0.3-12.0 years (Figure 8) was 14.2% (range; 3.4-29.4, standard deviation; 8.4), and the correlation coefficient between age and % ATNR was low (0.06, not significant). Accordingly, chin muscle atonia has been concluded to occur in a constant rate during NREM sleep in neurologically unaffected children. Chronological changes of % ATNR in my study [42] and Werth *et al.* [41] were not consistent with observations made by Petre-Quadens [40].

To determine the underlying mechanisms of % ATNR, correlation coefficients (r) between % ATNR and REM sleep indices in 25 neurologically unaffected children aged 0.3-12.0 years were calculated. Results demonstrated no significant correlation, although phasic muscle twitches during REM sleep (PCMA) tended to exhibit negative correlation with % ATNR ($r = -0.38$, $0.05<P<0.1$). PCMA occurrence correlated with the raphe nucleus unit discharges, where serotonergic neurons are located [43]. Hypoactivity of serotonergic neurons has been thought to contribute to elevated % ATNR values. In addition, elevated cholinergic activity produces muscle atonia during REM sleep [39]. Elevated % ATNR is hypothesized to be a result of decreased monoaminergic activity and/or increased cholinergic activity in the brainstem during NREM sleep. Petre-Quadens [40] demonstrated an elevated percentage of chin muscle atonia during NREM sleep in patients with mental retardation. Although anecdotal, we observed significantly increased % ATNR in a male patient with autism, who also had restless legs syndrome. In addition to the balance of activity between monoaminergic and cholinergic systems, other mechanisms responsible for determining % ATNR remain unknown.

Because increased % ATNR was reported in WS patients [44], we calculated % ATNR in twelve

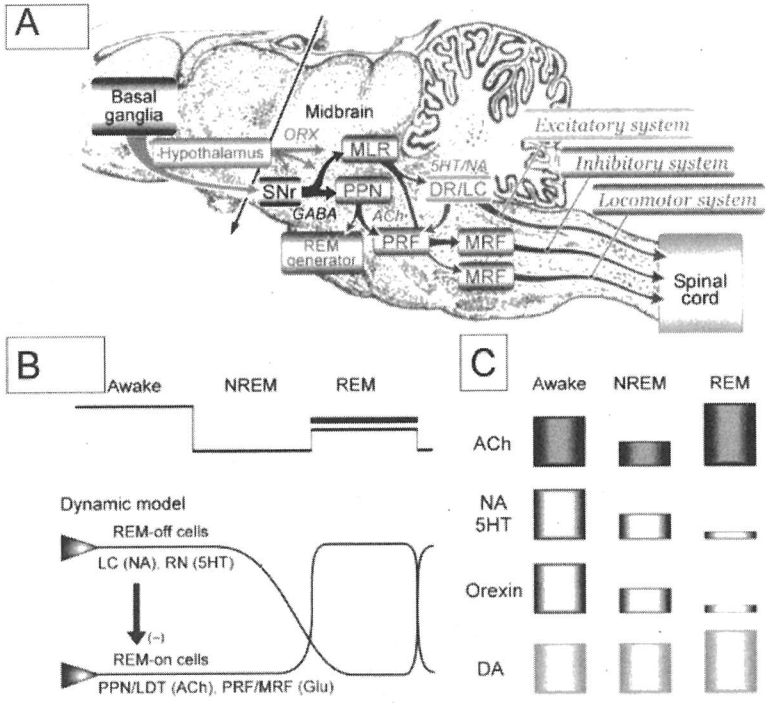

Figure 6. Schematic drawing of parasagittal brainstem section (A) and altered intrinsic chemical substances between states (B and C). A is from Fig. 3 in the manuscript by Takakusaki *et al.* [39] and B and C are from Fig. 4 in the same paper with permission. ORX: orexin; SNr: substantia nigra pars reticulate; MLR: midbrain locomotor region; PPN: pedunculopontine tegmental nucleus; PRF: pontine reticular formation; DR: dorsal raphe; LC: locus coeruleus; MRF: medullary reticular formation

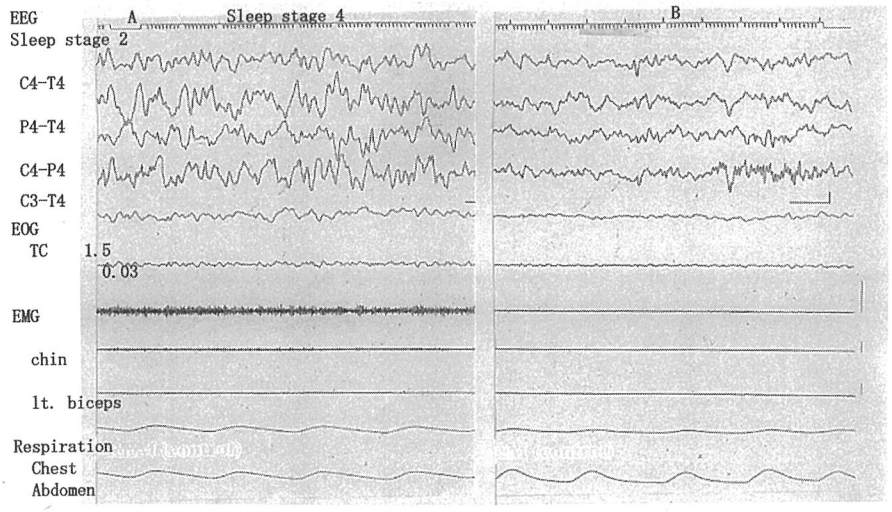

Figure 7. A is the polygraphic record during stage 4 sleep stage with sustained chin muscle activity, while B represents stage 2 sleep with decreased chin muscle activity.

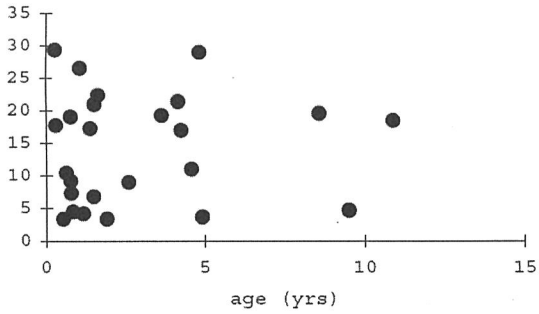

Figure 8. Percent ATNR values in 25 children aged 0.3-12.0 years. No obvious age-related changes were observed (cited from Fig. 3 in Kohyama [42] with permission).

untreated WS patients. Nine out of twelve patients exhibited good convulsion prognosis. Results were compared with age-matched, neurologically unaffected controls, demonstrating that mean % ATNR in WS patients was higher than in controls, although no significant difference was obtained.

5. Sleep health

To secure a sleep state under ideal conditions, health care providers should address the principles of sleep health. In addition, these principles should be applied to epilepsy patients. The four principles, as well as two additional points of sleep health, are shown in Table 2, with each principle based on neurological backgrounds [45, 46]. Diurnal cycle duration of the biological clock, which is located in the suprachiasmatic nucleus cycle, is longer than 24 hrs in most humans; this cycle can be shortened by light exposure after the body temperature trough is recorded in the morning to adjust to 24-hour cycle of the earth. However, light exposure prior to the body temperature trough (light exposure during night) increases cycle duration of the biological clock, which subsequently increases the original existing gap. The gap between the biological clock and the earth time results in conditions similar to jet lag [45, 46], which explains the first, third, and sixth issues of Table 2. In terms of the second issue, adequate physical, as well as mental, activity results in sufficient fatigue to fall asleep. The fourth issue was supported by a previous report demonstrating that the dorsomedial hypothalamic nucleus was a putative food-entrainable circadian pacemaker in mice. In addition, pacemaker oscillation persisted for at least two days, even when mice received no food during the expected feeding period following establishment of food-entrained behavioral rhythms [47].

Sleep neurology

Response-reversal is an example of motor phenomena that exhibits significant changes among states. However, it is not known why rapid eye movements appear during REM sleep, whereas slow eye movements occur during stage 1 sleep. In addition, it is not known why sleep spindles predominantly appear during stage 2 sleep or why we do not experience dreams we want to experience. Many aspects of neuronal activities during sleep remain to be elucidated. In addition, because a number of central nervous system abnormalities during sleep are expressed as abnormal movements, it is necessary to understand motor control during wakefulness, as well as during sleep. Moreover, recent technological advancements are expected to identify new indices that reflect brain activity, such as % ATNR.

Although anatomical connections in the central nervous system appear stable from a macro-structural viewpoint, functional connections affected by intrinsic chemical substances are remarkably altered among states. This modulation suggested different faces of each state, which was determined by the balance between intrinsic chemical substances. Epileptic disorders, which exhibit marked wake/sleep dependency, might be affected by these intrinsic circumstances.

Here, the author proposes a novel term "sleep neurology". This term is designated to promote the importance of sleep for neurologists. Some epileptic disorders exhibit significant wake/sleep dependency. Among many neurological disorders, epilepsy must be a useful medical condition to open paths for this novel, wide and fascinating research area of sleep neurology. Currently, sleep stages are defined by observations, but not neuronal activities in the brain. Sleep or sleep stage definitions could alter with research advancements in sleep neurology. A better understanding of sleep neurology is expected to promote basic, as well as clinical, investigations focused on phenomena observed during sleep.

Table 2. Principles of sleep health.

1	Increase exposure to morning light.
2	Engage in physical activity during daytime.
3	Sleep in the dark during the night (*i.e.*, turn off all artificial lighting).
4	Eat regular meals.
5	Avoid substances that disturb sleep (*e.g.*, caffeine, alcohol, nicotine).
6	Avoid excessive media exposure (*e.g.*, video games, computers, television).

CONCLUSION

Epilepsy is a useful disease condition to study the area of sleep neurology. Sleep neurology is a fascinating research area for many neurologists researching epilepsy.

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