

Chapter 2

Neurophysiology of Sleep

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Introduction

Consideration of the neurophysiological mechanisms of sleep and wakefulness emerged with the ability to measure “sleep” via the electroencephalogram (EEG), developed by Hans Berger in the 1920s–1930s. (Interestingly, this period overlaps Nathaniel Kleitman’s work on circadian rhythm published in 1929, which has been tied to sleep ever since.) The EEG clearly showed various patterns; the first being what Hans Berger described were “alpha” waves over the occipital cortex in awake relaxed humans with their eyes closed. In subsequent recordings, EEG synchrony was identified during the initial stages of sleep. Desynchronized or REM sleep was not discovered until 1953, when Aserinsky and Kleitman recorded people at night. Thus being able to distinguish EEG in wakefulness from sleep allowed scientists to address the neural origins of sleep.

Initial experiments began by addressing what EEG patterns were present in the isolated the central nervous system. Two preparations, *encephale isole* and *cerveau isole*, were created in cats. The *encephale isole* had the CNS transected near the caudal medulla, and the cats were kept alive on ventilators. Following this transection the cats went through oscillating periods of EEG synchrony and desynchrony. In contrast the *cerveau isole* is a transection through the midline separating the brainstem from the hypothalamus and cortex. Following this transection, the EEG was synchronized. One difference between the preparations was cranial sensory input, and the chronic EEG synchrony in the absence of sensory input resulted in deafferentation theory of sleep, sleep as a passive state resulting from the absence of

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sensory input. However, the other difference between the two preparations was the loss of brainstem structures. In the 1930s these were poorly defined, but since then many nuclei that determine state have been identified. In 1943, Moruzzi and Magoun identified the ascending reticular activating system (ARAS or RAS) and an area in the mesencephalon, which when selectively lesioned leaving the sensory pathways to the thalamus intact, synchronized the EEG, whereas when activated, desynchronized the EEG. This finding destroyed the passive theory of sleep – even though you as an individual do your best to reduce sensory input when you go to sleep by finding a warm comfortable place, turning off lights, and reducing noise.

The subsequent experiments combined recording activity and selective pharmacology with the lesioning and stimulation protocols to identify sites which are critical to state. Multiple sites have been identified that either promote wakefulness or promote sleep. Indeed, a current theory is that the balance between these mechanisms determines your state; ideally it is toggle switch, a “flip-flop” mechanism. The mutual inhibitory network between the wakefulness and sleep-promoting mechanisms ensures stable states. We present the material in this chapter to be consistent with both ACGME and ABIM requirements as both clearly mandate a comprehensive knowledge of the neural mechanisms underlying state.

The chapter will not be a review of the literature (See References 1–3) but will focus on findings that are fundamental to sleep practitioner’s knowledge and will provide specific examples of how topics in this area could be taught and then assessed for competency. Table 2.1 is a map of content domains showing how sub-topics may be related to the ACGME general competencies for training in sleep medicine. Table 2.2 lists examples of content-specific questions for generating learning objectives and for assessing the competency regarding these objectives. The raised questions can be the basis for instructional classes and incentives for journal club discussions.

This chapter also provides specific examples of assessment tools. The matching test is included to review factual knowledge of the neurophysiological basis of sleep. As knowledge develops in this field, questions can be added or modified. Essay questions are provided to assess an integrated understanding of an approach. These questions can be provided in many contexts and can be adopted to provide a direction of the discussion. The IQ cases offer examples of IQ group exercises, in which the learning objectives are disclosed later, requiring the learners to seek and evaluate information to achieve the learning objectives of the case. These group discussions assist learners to share knowledge and to improve their learning techniques. The IQ cases can assess where the group training is.

An illustrative PowerPoint is presented in a PDF format on the companion website (<http://competenciesinsleepmedicine.weebly.com/neurophysiology.html>). It may be reviewed by the student and the program or discussed in a group format before or after the essay questions or IQ case

State-specific neuronal discharge patterns		
Discharge type	Cell location	Transmitter
Wake-on/REM-off	DR, LC, PH	5HT, NE, HA
	LH	HCRT
REM-on	LDT/PPT	Ach
Wake-on/REM-on	LDT/PPT	Ach
	BF	
NREM-on	POA/AH/BF	GABA
State independent	VTa, SN	DA

Table 2.1 Cognitive Map of the Content Domains Relevant to the Neurophysiology of Sleep and Circadian Rhythm

		Knowledge	Skills	ACGME competency
I	<i>Epidemiology</i>	Yes	Yes	B, F
	Demographics			
	Risk factors			
	Special populations			
II	<i>Mechanisms</i>	Yes	Yes	A, B, E
	Central nervous system			
	Somatic nervous system			
III	Autonomic nervous system	Yes	Yes	A, B
	<i>Risk factors</i>			
	Psychiatric			
	Genetic/gender			
IV	Developmental/aging	Yes	No	A, C, F
	<i>Patient assessments</i>			
	Adult			
	Pediatrics			
V	Special populations	Yes	No	A, C, F
	<i>Diagnostic measures and interpretation</i>			
	Polysomnography			
	History and physical examination			
VI	Patient-based testing	Yes	Yes	A, E, D, F
	<i>Disease management</i>			
	Decisions on therapy			
	Type of therapy			

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		Knowledge	Skills	ACGME competency
VII	<i>Health and disease clinical pathways</i>	Yes	Yes	A, C, F
	Neural disorders			
	Psychiatric disorders			
	Medical comorbidities			
	<i>Code for ACGME competencies</i>			
	A. Patient care		D. Interpersonal skills	
	B. Medical knowledge		E. Professionalism	
	C. Practice-based learning and improvement		F. System-based practice	

Table 2.2 Examples of Topics with Educational Objectives*Item I. Genetics*

- Define genetic functional systems in sleep and wakefulness – GABA, orexin, and monoamines
- Become familiar with the terminology of neuroscience of sleep:
 1. Brain structures: suprachiasmatic nucleus (SCN), ventrolateral preoptic area (VLPO), tuberomammillary nucleus (TMN), subparaventricular zone (SPZ), dorsomedial nucleus of the hypothalamus (DMH), pedunculopontine tegmentum/lateral dorsal tegmentum (PPT/LDT), retinohypothalamic tract (RHT), dorsal raphé, locus coeruleus, medial pontine reticular formation, ascending reticular activating system, lateral hypothalamus, inhibitory area of Magoun and Rhines, peri-locus coeruleus area
 2. Neurotransmitters: melatonin, orexin (hypocretin), GABA, serotonin (5HT), acetylcholine (ACh), histamine, adenosine, catecholamines, histamine, monoamines
 3. Effective drugs: modafinil, armodafinil, benzodiazepines, almorexant, Rozerem (ramelteon), Lunesta (eszopiclone), longdaysin
- List how proteins affect cortical membrane potential, hyperpolarizing versus depolarizing

Item II. Anatomy and physiology

- Describe the location and role of the hypothalamus (ventrolateral preoptic (VLPO), ventrolateral hypothalamus, pedunculopontine tegmentum/lateral dorsal tegmentum (PPT/LDT), reticular activating system (RAS)
- Understand the balance of excitatory and inhibitory input in controlling thalamocortical loops
- Understand the difference in the neurophysiologic basis between NREM and REM sleep
- Understand the control of motor activity during REM sleep

Item III. Clinical syndromes

- Describe from a neural systems viewpoint
 - Narcolepsy
 - Insomnia
 - Restless legs syndrome
 - REM sleep disorders
 - Sleep apnea

Item IV. Diagnostic measures as a reflection of circadian and sleep neural systems

- Multiple sleep latency onset
- Questionnaires
- Polysomnography (especially EMG)

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Item V. Therapeutics

- Drug actions that promote wakefulness (modafinil, armodafinil)
- Drug actions that promote sleepiness (benzodiazepines, nonbenzodiazepines)
- Drugs actions that treat cataplexy (tricyclic antidepressant, sodium oxybate)

Item VI. Prognosis, complications, and comorbid conditions

- Discuss interactions of sleep neural systems with pathophysiologic and treatments for primary neurologic and psychiatric disorders
 - Understand the interaction of drug addiction and recovery and sleep neurophysiology
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Matching Test

Questions

The sleep-promoting actions of this neurotransmitter are antagonized by caffeine.

These neurons release the inhibitory neurotransmitters galanin and GABA to inhibit the monoaminergic cell groups in the locus coeruleus, the raphe nucleus, and the tuberomammillary nucleus.

This hypothalamic region is critical for the integrating circadian rhythms of sleep-wakefulness, feeding, locomotion, and temperature.

G-protein-coupled receptor that binds both orexin A and orexin B and is present mainly in GABAergic putative brainstem interneurons.

This neurotransmitter is synthesized in raphe neurons whose activity varies with state greatest in wakefulness and least in REM sleep.

This brainstem region contains serotonergic cells that become quiescent during REM sleep.

Its release in the cortex is high during waking and REM sleep and lowest during deep NREM sleep.

This brainstem structure described in 1949 receives input from many sensory modalities and sends output to the thalamus and cortex. Its activity is state dependent.

Synthesized in tuberomammillary nuclei of the posterior hypothalamus, this neurotransmitter is released extensively throughout the brain.

Arousing neurotransmitter; formed in the CNS by tuberomammillary neurons in the posterior hypothalamus.

This brainstem region contains neurons that are active during, and may even initiate, REM sleep.

Stimulation of this cranial nerve is hypnogenic.

A hormone synthesized in the paraventricular nucleus of the hypothalamus which is released in response to stress.

Nearly 50 years before the description of REM sleep, it has been known that carbachol administered to this brainstem area produced a state change which we now refer to as “REM-like.”

This structure is critical for integrating sleep and metabolism physiologically and behaviorally.

A drug that enhances the action of GABA at the GABAA receptor and promotes sleep.

Medullary area which mediates muscle atonia.

A class of neurotransmitters with an amino group connected to an aromatic ring. Examples include histamine, catecholamines (dopamine, norepinephrine, and epinephrine), and tryptamines (serotonin (5-HT) and melatonin).

This brainstem nucleus contains norepinephrine neurons that are active during wakefulness.

Bilateral lesions in this pontine area result in animals “acting out” their dreams.

This hypothalamic structure is critical for determining circadian rhythm.

The circadian rhythm of this hormone’s levels is disrupted by light in the blue-light wavelength (~440 nm).

Loss of this nucleus after bilateral destruction of the posterior hypothalamus results in hypersomnolence.

Deficiency in this neuropeptide modulator underlies the most common form of narcolepsy, in which the sufferer briefly loses muscle tone (cataplexy).

This hypothalamic nucleus receives a strong projection from the SCN and contains subnuclei that regulate circadian rhythms of body temperature and sleep separately.

Answers

1. Suprachiasmatic nucleus (SCN)
2. Ventrolateral preoptic area (VLPO)
3. Tuberomammillary nucleus (TMN)
4. Paraventricular nucleus
5. Subparaventricular zone (SPZ)
6. Dorsomedial nucleus of the hypothalamus (DMH)
7. Pedunculopontine tegmentum/lateral dorsal tegmentum (PPT/LDT)
8. Retinohypothalamic tract (RHT)
9. Median preoptic nucleus
10. Dorsal raphe
11. *Locus coeruleus*
12. Kölliker-Fuse nucleus
13. Medial pontine reticular formation
14. Ascending reticular activating system
15. Pineal body
16. Lateral hypothalamus
17. Inhibitory area of Magoun and Rhines
18. Peri-locus coeruleus α area
19. Pontine gray
20. Vagus
20. Vagus
21. Melatonin
22. Orexin (hypocretin)
23. Orexin 1 receptors
24. Orexin 2 receptors
25. GABA
26. Glycine
27. Serotonin (5HT)
28. Acetylcholine (ACh)/cholinergic
29. Histamine
30. Adenosine
31. A1 receptors
32. A2 receptors
33. Caffeine
34. Epinephrine/catecholamines
35. Histamine
36. Monoamines
37. Catecholamines
38. Excitatory amino acids
39. Benzodiazepine
40. Corticotrophin-releasing factor

Questions with Answers

- The sleep-promoting actions of this neurotransmitter are antagonized by caffeine. 30
- These neurons release the inhibitory neurotransmitters galanin and GABA to inhibit the monoaminergic cell groups in the *locus coeruleus*, the raphe nucleus, and the tuberomammillary nucleus. 2
- This hypothalamic region is critical for the integrating circadian rhythms of sleep-wakefulness, feeding, locomotion, and temperature. 6
- G-protein-coupled receptor that binds both orexin A and orexin B and is present mainly in GABAergic putative brainstem interneurons. 24
- This neurotransmitter is synthesized in raphe neurons whose activity varies with state greatest in wakefulness and least in REM sleep. 27
- This brainstem region contains serotonergic cells that become quiescent during REM sleep. 10
- Its release in the cortex is high during waking and REM sleep and lowest during deep NREM sleep. 28
- This brainstem structure described in 1949 receives input from many sensory modalities and sends output to the thalamus and cortex. Its activity is state dependent. 14
- Synthesized in tuberomammillary nuclei of the posterior hypothalamus, this neurotransmitter is released extensively throughout the brain. 29
- Arousing neurotransmitter; formed in the CNS by tuberomammillary neurons in the posterior hypothalamus. 35
- This brainstem region contains neurons that are active during, and may even initiate, REM sleep. 7
- Stimulation of this cranial nerve is hypnogenic. 20
- A hormone synthesized in the paraventricular nucleus of the hypothalamus which is released in response to stress. 40
- Nearly 50 years before the description of REM sleep, it has been known that carbachol administered to this brainstem area produced a state change which we now refer to as “REM-like.” 13
- This structure is critical for integrating sleep and metabolism physiologically and behaviorally. 16
- A drug that enhances the action of GABA at the GABAA receptor and promotes sleep. 39
- Medullary area which mediates muscle atonia. 17
- A class of neurotransmitters with an amino group connected to an aromatic ring. Examples include histamine, catecholamines (dopamine, norepinephrine, and epinephrine), and tryptamines (serotonin (5-HT) and melatonin). 36
- This brainstem nucleus contains norepinephrine neurons that are active during wakefulness. 11
- Bilateral lesions in this pontine area result in animals “acting out” their dreams. 18
- This hypothalamic structure is critical for determining circadian rhythm. 1

The circadian rhythm of this hormone's levels is disrupted by light in the blue-light wavelength (~440 nm). 21

Loss of this nucleus after bilateral destruction of the posterior hypothalamus results in hypersomnolence. 3

Deficiency in this neuropeptide modulator underlies the most common form of narcolepsy, in which the sufferer briefly loses muscle tone (cataplexy). 22

This hypothalamic nucleus receives a strong projection from the SCN and contains subnuclei that regulate circadian rhythms of body temperature and sleep separately. 5

Essay Questions

Familial Advanced Sleep Phase Syndrome (FASPS)

A 22-year-old male complains of early morning (~4:00 am) waking and difficulty to go back to sleep. He usually gets out of bed at 5:00 am. The early waking cannot be explained by anxiety regarding the day's commitments or by jet lag, recent travel crossing time zones. He is energized and performs well in the morning. However, his energy runs out much earlier than what he expected in the afternoon. He does not watch TV or movies in the evening due to difficulty in maintaining wakefulness after 7:30 pm. He has to go to bed at 8:30 pm. This started several years ago but over the past 2 years has worsened. Otherwise he is generally healthy and has maintained a good GPA at both high school and college. He knows that his father and one of his cousins have the similar problem. His Horne-Östberg score was 75. His Morningness-Eveningness Questionnaire (MEQ) showed he is M-type.

Questions

1. What is the most likely diagnosis?
2. How may patient's melatonin phase change?
3. What gene mutation may patient have?
4. What are the treatments and their long-term effectiveness/outcome?

Answers

1. *Familial advanced sleep phase syndrome (FASPS)*: Patients with FASPS have about a 4-h phase advance, which causes arousal in the morning and sleep onset in the evening earlier than normal population. In general, patients arouse at 4–5:30 am and fall to sleep at 7:30–8:30 pm. Although their biological rhythms and major sleep timing are all advanced, they are in phase with each other much like healthy controls. FASPS has familial factors. The complaints of early waking and sleeping and the similar symptoms of their family members are a good indication of FASPS.
2. The patient's dim-light melatonin onset (DLMO) should be phase-advanced by 3–4 h. This phase change should be distinguished from changes due to stress, sleep deprivation, or unconventional sleep-wake schedules.
3. The patient may have either hPER2 or CK1 gene mutation. In this scenario, CLOCK and BMAL1 are transcriptional factors that heterodimerize and induce the expression of *Per* and *Cry* genes by binding to their promoters at E-boxes. CK1 isoforms bind and phosphorylate PER and CRY and subsequently cause the degradation of Clock/Bmal1 stopping the transcription of *Per* and *Cry*. Recently, a missense mutation at a putative phosphorylation site in hPER2, Ser-662, was identified in patients that suffer from FASPS. This is a serine-to-glycine point mutation in the CK1 binding domain of the hPER2 protein that resulted in hypo-phosphorylation of PER2 in vitro. Interestingly, a mutation of CK1δ was found separately in Japanese family that suffers from FASPS as well.
4. ASPD can be treated with bright light therapy in the evenings or behaviorally with chronotherapy. Unlike other sleep disorders, ASPD does not disrupt normal

functioning at work during the day, and the patient does not complain of excessive daytime sleepiness. If their ASPD is causing patients to miss evening activities, including putting their own normal children to bed, then with this treatment they can stay awake later than their circadian rhythm. A sufferer of ASPD will still wake very early, and if this cycle continues, it can lead to chronic sleep deprivation and other sleep disorders.

Neurophysiology of Sleep and Circadian Rhythm

A 16-year-old male finds it hard to function at school and home and in social situations because of extreme tiredness. He has trouble sleeping at night, but can fall asleep suddenly, even in the middle of talking, eating, or other activity. When he falls asleep suddenly, he suffers loss of muscle tone. Strong emotions can often trigger these episodes, which may last seconds or minutes.

Questions

1. What is the most likely diagnosis?
2. What are the probable neurophysiologic pathways that are disrupted to cause narcolepsy?
3. How do treatment strategies intervene in these probable pathways?
4. What neurophysiologic pathways control muscle atonia during REM sleep?

Answers

1. Narcolepsy, which is a disorder that causes periods of extreme daytime sleepiness. The disorder also may cause muscle weakness.
2. Orexin-producing neurons in the lateral posterior hypothalamic nuclei (perifornical area, lateral hypothalamus, and posterior hypothalamus). These “orexin” neurons activate monoaminergic neurons in the hypothalamus (tuberomammillary nucleus) and brainstem (raphe, locus coeruleus) that promote wakefulness.
3. Treatment strategies depend on the differential symptoms of sleepiness and cataplexy. Excessive daytime sleepiness (sleep attacks) is responsive to stimulant medications that promote wakefulness. Modafinil (Provigil) has FDA approval for the treatment of narcolepsy and may act as an agonist of the orexin receptors. Sodium oxybate (Xyrem) is approved for use in the treatment of narcolepsy to reduce cataplexy and excessive daytime sleepiness (EDS).
4. Muscle atonia results from two complementary mechanisms: disfacilitation, decreased noradrenergic and serotonergic excitatory input, and inhibition, glycinergic and GABAergic inputs hyperpolarizing the membrane (making the membrane potential more negative). Both disfacilitation and inhibition are brainstem mechanisms that can be elicited by acetylcholine placed in the brainstem. Disfacilitation results from the loss of noradrenaline from locus coeruleus and serotonin from caudal raphe. These neuronal transmitters decrease because activity of the groups is state dependent and decreases in REM sleep. On the other hand, stimulation of the inhibitory area of Magoun and Rhines in the medullary reticular formation mediates inhibition in REM sleep. These pathways are involved in the muscle atonia of REM sleep.

IQ Case

Evaluate Neurophysiology of Sleep and Diagnosis of Insomnia for Student

Goal: Understand the tools, especially how with an available history and clinical data one can utilize knowledge of the neurophysiology of sleep.

Case Vignette

Insomnia description: A 22-year-old girl is self-referred to the sleep clinic because she has been unable to fall asleep every night for several years. She also cannot maintain a good sleep during the night due to frequent waking up. This could be a self-wakening up or waking up by gentle noise. She finds it very difficult to go back to sleep again if she wakes up. She said she dreamed a lot and she can remember almost everything that happened during the night. When she goes to school in the morning, she feels tired. She is in her last year of college and majors Biology. She feels nervous about exams. The sleep problem would be worsened if she has an important schedule the next day. Sometimes she feels sad and lonely and is not interested in any classes, but that is not often and lasts very briefly. Her GPA was 3.7 in high school and is around 3.3 currently.

The predominant complaint of primary insomnia is difficulty initiating or maintaining sleep, or nonrestorative sleep, for at least 1 month. This may cause significant distress in the daytime or during work and impact social or occupational functioning. The sleep disturbance may associate with daytime fatigue and be worsened by stress overloading. Primary insomniacs do not have a history of substances usage or diagnosis of mood disorders. However, literature reports that chronic insomnia may lead to depressive disorders.

Major symptom of insomnia is difficulty in falling asleep and maintaining sleep. Thus, patient may have extended sleep latency, increased number of wakefulness after sleep onset, reduced total sleep, and decreased deep sleep such as N3. If the power spectral density of the EEG is analyzed, the delta power band may be decreased. This could be partially reflected in the PSQI and should have all in the PSG data. Patients diagnosed with primary insomnia should have a normal PHQ-2.

Insomnia is a highly prevalent sleep disorder, yet little is known about the role of genetic factors in its pathophysiology. Primary insomnia may have PSG hyperarousal and elevated hypothalamic-pituitary-adrenal (HPA) axis. Elevated brain level of CRF or orexins may be involved. However, there is no literature regarding the measurement of CSF orexin levels in primary insomniacs. Primary insomnia has to be treated individually and can be treated with cognitive behavioral therapy such as reducing usage of caffeine, tobacco, or alcohol near bedtime and avoiding daytime sleep. Antidepressant trazodone has been selected as the initial treatment in a considerable percentage of patients. Newer classes of benzodiazepine and nonbenzodiazepine are also used substantially. Primary insomnia is treatable but may be difficult to cure.

Evaluate Neurophysiology of Sleep and Diagnosis of Insomnia for Facilitator

Goal: Understand the instrument available for the examination and assessment of sleep quality and how to interpret them.

Objectives (Revealed at the End of the Session)

- A. Describe the different sleep states and their neurophysiologic basis.
- B. Interpret polysomnography (EEG, EOG, EMG, and cardiorespiratory) patterns.
- C. Discuss the neurophysiologic basis of common sleep disorders.
- D. Describe the impact of disturbed sleep on patient's quality of life.
- E. Propose a diagnostic plan to properly assess the neurologic function in sleep disorders.

Case Vignette

Insomnia description: A 22-year-old girl is self-referred to the sleep clinic because she has been unable to fall asleep every night for several years. She also cannot maintain a good sleep during the night due to frequent waking up. This could be a self-wakening up or waking up by gentle noise. She finds it very difficult to go back to sleep again if she wakes up. She said she dreamed a lot and she can remember almost everything that happened during the night. When she goes to school in the morning, she feels tired. She is in her last year of college and majors Biology. She feels nervous about exams. The sleep problem would be worsened if she has an important schedule the next day. Sometimes she feels sad and lonely and is not interested in any classes, but that is not often and lasts very briefly. Her GPA was 3.7 in high school and is around 3.3 currently.

Probing Questions

- 1. What kind of sleep disorder is most probable?
- 2. What conditions may predispose to this disorder?
- 3. What complications may arise from this if left untreated?
- 4. How would you proceed with a diagnostic plan?

The predominant complaint of primary insomnia is difficulty initiating or maintaining sleep, or nonrestorative sleep, for at least 1 month. This may cause significant distress in the daytime or during work and impact social or occupational functioning. The sleep disturbance may associate with daytime fatigue and be worsened by stress overloading. Primary insomniacs do not have a history of substances usage or diagnosis of mood disorders. However, literature reports that chronic insomnia may lead to depressive disorders.

Probing Questions

5. What do the PSQI (Pittsburgh Sleep Quality Index) and PHQ-2 (Patient Health Questionnaire-2) show?
6. What do the multiple sleep latency test and polysomnography show?
7. What is your diagnosis based on the PSQI and polysomnography?
8. What is the concordance between PSQI and polysomnography?

The major symptom of insomnia is difficulty in falling asleep and maintaining sleep. Thus, the patient may have extended sleep latency, increased number of wakefulness after sleep onset, reduced total sleep, and decreased deep sleep such as N3. If analyzed using EEG power frequency, the delta power band may be decreased. This could be partially reflected in the PSQI and should have all in the PSG data. Patients diagnosed with primary insomnia should have a normal PHQ-2.

Probing Questions

9. What can you tell the patient about inheritability?
10. What is the chance of successful treatment?
11. How can you reduce the chance of other sleep and psychiatric disorders from developing?

Insomnia is a highly prevalent sleep disorder, yet little is known about the role of genetic factors in its pathophysiology. Primary insomnia may have PSG hyperarousal and elevated hypothalamic-pituitary-adrenal (HPA) axis. Elevated brain level of CRF or orexins may be involved. However, there is no literature regarding the measurement of CSF orexin levels in primary insomniacs. Primary insomnia has to be treated individually and can be treated with cognitive behavioral therapy such as reducing usage of caffeine, tobacco, or alcohol near bedtime and avoiding daytime sleep. Antidepressant trazodone has been selected as the initial treatment in a considerable percentage of patients. Newer classes of benzodiazepine and nonbenzodiazepine are also used substantially. Primary insomnia is treatable but may be difficult to cure.

Probing Questions

12. What is the long-term efficacy of treatment?
13. What other insomnia disorders can you name?

Evaluate Neurophysiology of Sleep and Diagnosis of Insomnia: Final Handout/Objectives

Goal: Understand the instrument available for the examination and assessment of sleep quality and how to interpret them.

Objectives (Revealed at the End of the Session)

- A. Describe the different sleep states and their neurophysiologic basis.
- B. Interpret polysomnography (EEG, EOG, EMG, and cardiorespiratory) patterns.
- C. Discuss the neurophysiologic basis of common sleep disorders.
- D. Describe the impact of disturbed sleep on patient's quality of life.
- E. Propose a diagnostic plan to properly assess the neurologic function in sleep disorders.

Evaluation of Neurophysiology of Sleep for Student**Case Vignette**

A 53-year-old man is at the sleep clinic because since the age of 44 he has been unable to fall asleep easily. When he goes to bed at night, he feels urges to move his legs due to uncomfortable sensations coming from his legs. Stretching and even just moving the legs brings temporary relief. However, walking for an extended period before going to bed effectively relieved these urges in the past, but it has gotten progressively less effective. Further, on long plane trips or long classical music concerts, he has to get up and walk around to relieve the discomfort. In the morning, he doesn't have these symptoms while lying in bed. He is physically fit with no other apparent medical problems.

Restless legs syndrome (RLS) or Willis-Ekbom disease: Surprisingly up to 10 % of the US population may have RLS, but most have a mild form of the disorder that is relieved by physical activity and is intermittent. Nevertheless severe, sleep disruptive RLS affects millions of individuals. Support groups have formed a website: <http://www.rls.org>.

The patient is diagnosed with restless legs syndrome (RLS) or Willis-Ekbom disease based on self-reported symptoms and the absence of causes due to vitamin or iron (serum ferritin) deficiencies, vascular insufficiency, and thyroid hormone abnormalities. No specific test exists for restless legs syndrome; rather eliminate secondary, highly treatable causes of RLS.

More than 60 % of cases of RLS are inherited in an autosomal dominant fashion with variable penetrance (Lavigne and Montplaisir 1994). Treatment is first to reduce symptoms and second, if necessary, pharmacologic. Many drug treatments have been proposed; one discussed on the restless legs website is ropinirole, a dopaminergic agonist. Interestingly in states that have medical marijuana laws, RLS is a treatable illness.

Evaluation of Neurophysiology of Sleep for Facilitator

Goal: Understand the tools, especially history available to evaluate of neurophysiology of sleep and how to interpret the data.

Objectives (Revealed at the End of the Session)

- A. Describe the neurophysiologic basis of motor control during different sleep states.
- B. Interpret EMG and what other measurement can be used to confirm the EMG findings.
- C. Discuss the neurophysiologic basis of NREM sleep and disorders associated with movement during NREM sleep.
- D. Discuss the neurophysiologic basis of REM sleep and disorders associated with movement during REM sleep.

Case Vignette

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Probing Questions

- 1. What kind of sleep disorder is most probable?
- 2. What conditions may predispose to this disorder?
- 3. What complications may arise from this if left untreated?
- 4. How would you proceed with a diagnostic plan?
- 5. What would you say to the sufferer? What is the prevalence? What is the success of treatment?

Restless legs syndrome (RLS) or Willis-Ekbom disease: Surprisingly up to 10 % of the US population may have RLS, but most have a mild form of the disorder that is relieved by physical activity and is intermittent. Nevertheless severe, sleep disruptive RLS affects millions of individuals. Support groups have formed a website: <http://www.rls.org>.

Probing Questions

- 6. Are there specific tests for this disorder? What will polysomnography show?
- 7. On what is your diagnosis based?
- 8. Would blood tests help?

The patient is diagnosed with restless legs syndrome (RLS) or Willis-Ekbom disease based on self-reported symptoms and the absence of causes due to vitamin or iron (serum ferritin) deficiencies, vascular insufficiency, and thyroid hormone abnormalities. No specific test exists for restless legs syndrome; rather eliminate try to secondary, highly treatable causes of RLS.

Probing Questions

9. What can you tell the patient about inheritability?
10. What is the chance of successful treatment?
11. What other sleep disorders are associated with this disease?

More than 60 % of cases of RLS are inherited in an autosomal dominant fashion with variable penetrance (Lavigne and Montplaisir, 1994). Treatment is first to reduce symptoms and second, if necessary, pharmacologic. Many drug treatments have been proposed; one discussed on the restless legs website is ropinirole a dopaminergic agonist.

Probing Questions

12. What is the long-term efficacy of treatment?
13. What other motor control disorders associated with sleep and its stage?

Evaluation of Neurophysiology of Sleep: Final Handout/ Objectives

Goal: Understand the tools, especially history available to evaluate of neurophysiology of sleep and how to interpret the data.

Objectives (Revealed at the End of the Session)

- A. Describe the neurophysiologic basis of motor control during different sleep states.
- B. Interpret the EMG and find other signals to confirm EMG findings.
- C. Discuss the neurophysiologic basis of NREM sleep and disorders associated with movement during NREM sleep.
- D. Discuss the neurophysiologic basis of REM sleep and disorders associated with movement during REM sleep.

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