Physiology and Neurochemistry of Sleep

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INTRODUCTION

Human Physiology is the foundation upon which all courses related to the health professions build. Pharmacy students, in their eagerness to advance to the courses more specifically related to their field, may be impatient and want to give less attention to the basic sciences. However, pharmacy students must have a solid working knowledge of the human body and the ailments that befall it before they can begin to understand the effects of pharmaceuticals.

In teaching physiology to pharmacy students, it is important to make the subject matter relevant to the student's lives. Finding examples which allow the students to reflect on their personal experiences is usually easy when teaching physiology. It is also important to relate subjects in physiology to other topics which are relevant to the study of pharmacy. To understand sleep, for example, the pharmacy student needs to consider concepts related to anatomy, physiology, pharmacology, pathophysiology, as well as neuroscience. Fortunately, students have years of first-hand experience observing their own sleep behaviors and can relate this experience to the classroom experience. The following is the summary of a lecture on sleep which is usually given to pharmacy students at the end of their first year in the College of Pharmacy at the University of Florida.

SLEEP

Sleep is a very important drive. Studies performed on rats at the University of Chicago suggest that total sleep deprivation leads to death within weeks(1). Sleep is also an insistent drive; while people can deprive themselves of food and water until they die, a person cannot voluntarily sleep deprive themselves to death. Indeed, people will drift into sleep, even if they are in a situation (*i.e.,* driving a car) in which sleeping will mean their death.

It is extremely important for pharmacists to understand the basic phenomena of sleep. Many drugs have an affect on sleep, either directly (benzodiazepines, barbiturates, stimulants) or indirectly (opiates, melatonin). At least four of the top 10 drugs prescribed have some effect on sleep(2).

BASICS OF THE SLEEP CYCLE

Sleep is divided into REM Sleep and Non-REM (NREM) sleep. REM sleep (rapid eye movement) is sometimes referred to as "dream sleep," although dreams can occur at any stage in the sleep cycle. NREM sleep consists of stages 1,2,3 and 4. REM and NREM stages are characterized by EEG (electroencephalogram) measurements, as well as by other physiological correlates such as the EMG (electromyogram) and the EOG (electro-oculogram).

The EEG measures small changes in voltage between electrodes placed on the scalp. EEG doesn't measure the discharge of a single neuron, rather it measures the summed postsynaptic potential of large portions of nervous tissue. Waves are measured for changes in duration (frequency) and in amplitude. Waves are categorized as either synchronized or desynchronized. Synchronized waves are high amplitude, low frequency waves. They are seen during NREM sleep and represent a coactivation of a large number of neurons. Desynchronized waves are seen when the brain is very active (*i.e.,* during wakefulness and REM sleep) and are low amplitude, high frequency waves.

In addition to the electroencephalogram, EMG and EOG are often used in sleep labs to give information about the sleep cycle. EOG measures eye movements. During REM sleep, you can observe the rapid eye movements that give REM sleep its name. EMG measures muscle activity. It is highest during wakefulness, lower during NREM sleep, and, except for occasional twitches, flat during REM sleep, as muscle atonia occurs during REM sleep. Muscle atonia is a characteristic of REM sleep that has been utilized by sleep researchers in order to preferentially deprive lab animals of REM sleep. The "flowerpot" technique involves placing an animal (*i.e.,* a rat) on top of an upside down flower pot in a bucket of water. The rat has ample room when he is awake, and can enter NREM sleep, but as soon as he enters REM sleep, he loses muscle tone, falls off the flowerpot, and splashes down into the bucket of water. He soggily and grumpily climbs back up onto his flowerpot, and goes back into NREM sleep. During the next entry into REM sleep, he's back in the water. Thus he is preferentially deprived of REM sleep.

SLEEP CYCLE

Sleep is divided into a 90 minute cycle of NREM sleep and REM sleep. This cycle is repeated 3-6 times during the night. Generally, a night of sleep begins with about 80 minutes of NREM and 10 minutes of REM sleep. As the sleep cycle progresses through the night there is less stage 3,4 NREM sleep and more REM sleep. Thus, there is more REM sleep on towards morning, which explains why when you awaken in the morning, you generally awaken from a dream.

Wakefulness. There are two main types of EEG waves during wakefulness. Beta waves are desynchronized; low voltage (low amplitude), and of a high-mixed frequency. They are seen when the patient is alert and engaged. Alpha waves are low voltage, mixed frequency waves, and are more synchronous than beta waves. They are seen when then subject is relaxed or drowsy, with their eyes closed.

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NREM Sleep. NREM sleep is divided into stages 1,2,3, and 4. As you progress through stages 1-4, the sleep gets "deeper" (*i.e.,* exhibiting a higher arousal threshold) and the waves become more synchronized.

Stage 1 sleep is a very light stage of sleep with a low arousal threshold. It generally lasts for less than 10 minutes, at sleep onset. During this stage, the EEG shows alpha activity. During stage 2 sleep, which accounts for 50 percent of total sleep time, the EEG shows low-voltage activity. The frequency is mixed, but slowing. The EEG during stage 2 sleep also shows "sleep spindles," which are slow, sinusoidal waves with bursts of high amplitude peaks. Hypnotic agents have been shown to increase the density of sleep spindles.

Stage 3,4 sleep, which is sometimes called Slow Wave Sleep, accounts for 15 percent of total sleep time. During Slow Wave Sleep, the EEG is synchronized. At this stage the waves are called Delta waves; they are of a high amplitude and low frequency. During slow wave sleep, we see the highest auditory arousal threshold, especially in children. One study showed that an auditory signal of 120 dB (comparable to the sound of a jet engine form 500 feet) was inadequate to wake school aged children (3). This auditory arousal has been shown to depend on the stimuli. If the stimulus is significant to the subject, they are more likely to awaken. For instance, a subject is more likely to awaken to the sound of her own name than to another name, or more likely to awaken to the sound of her own baby crying, rather than to the sound of another baby(3).

REM Sleep. REM sleep generally makes up 20-25 percent of total sleep time in adults. In infants, REM sleep (or active sleep, as it is called in newborns) may account for up to 50 percent of sleep. Since total sleep time decreases in the elderly, the total amount of REM sleep may also fall. The absolute amount of REM sleep has been correlated with intellectual functioning in the elderly(4); REM sleep levels are shown to be diminished in Alzheimer's patients(5).

REM sleep consists of tonic characteristics and phasic characteristics. Tonic characteristics are persistent throughout the entire REM sleep period, while phasic characteristics appear intermittently during the REM sleep period. Tonic characteristics include a desynchronized EEG, muscle atonia and a lack of thermoregulation. Phasic characteristics include rapid eye movements, PGO waves, clitoral and penile tumescence and dreams.

Tonic Characteristics. During REM sleep, the EEG is desynchronized (low voltage, high-mixed frequency), as it is during wakefulness. Shakespeare may have described dreams as "the children of an idle brain," but in actuality, many areas of the brain are very active during REM sleep: the visual cortex, limbic lobe and hippocampus in particular. Cerebral blood flow is also high during REM sleep.

Muscle atonia is a characteristic of REM sleep. Except for random twitches, skeletal muscles (except for the ocular muscles and the diaphragm) are completely relaxed. This is due to postsynaptic inhibition of motor neurons and membrane hyperpolarization. In subjects with pontine damage, REM without atonia can occur. These patients physically enact the events of their dreams. One case study sites a 77 year old minister who had frequent "fighting dreams" and whose wife has sustained repeated blows due to her husband's vigorous sleep movements(6). Therefore, sleep walking and sleep talking are actually NREM sleep phenomenon, since muscle tone goes flat during REM sleep.

During REM sleep cells in the preoptic/anterior hypothalamus which control thermoregulation cease firing, making us essentially poikilothermic creatures during REM sleep(7). Since our thermoregulatory cells stop firing during REM sleep, our body temperatures tend to approach ambient temperature. Similarly, at extremes in ambient temperature, REM sleep is lost. Animals kept at ambient temperatures in the thermoneutral zone, "that range of ambient temperatures at which the basal rate of heat production equals the rate of heat loss to the environment"(8) show maximal levels of REM sleep.

One of the best known phasic characteristics of REM sleep are the rapid eye movements for which the sleep state is named. Eye movements usually do not follow the action of the dream, except in some situations *(i.e.,* dreaming of a tennis match). PGO waves are a phasic burst of electrical activity between pons, lateral geniculate nucleus of the thalamus and the occipital cortex. Their exact role is unknown, although they may have a pacemaker role in the other phasic actions of REM sleep, such as rapid eye movements. They begin during NREM and may herald the onset of REM sleep.

Clitoral and penile tumescence occur during REM sleep. Most REM sleep occurs towards morning; this helps to explain the erections which accompany awakening in the morning. The erections that occur during REM sleep are not necessarily related to dream content, they are just a physiological correlate of the sleep state. It does provide a useful tool for assessing impotence in males. Since erections occur involuntarily during REM sleep, it is possible to assess whether impotence is physiological or psychological. Subjects may go to a sleep lab (or may monitor themselves at home) and monitor nocturnal penile tumescence.

Finally, dreams. While dreams are what people most often associate with REM sleep, a person is not always dreaming while they are in REM sleep; dreams occupy approximately 80-90 percent of REM sleep. Also, not all dreams are REM sleep dreams. Studies from sleep labs have shown that dreaming can occur during wakefulness and NREM sleep, as well as during REM sleep. Generally, REM dreams are longer, more visual, more bizarre, and not as related to actual life events. Those dreams in which Elvis is skateboarding with your mother but it's not really your mother, it's really your cat, and suddenly Elvis has turned into Bullwinkle, although he still sings very well, is probably a REM sleep dream. Or incipient mental illness. NREM dreams tend to be shorter, more thoughtful, less emotional and more related to life events. These are the types of dreams in which you think about the Henderson-Hasselbach equation all night long. Also, nightmares and night terrors occur during NREM sleep.

PHYSIOLOGICAL CHANGES DURING SLEEP

Cardiovascular. During NREM, there is an overall reduction in heart rate, cardiac output and blood pressure, due to a general vasodilation. During REM sleep, there are variations in blood pressure and heart rate, but overall the rates are increased, especially during the phasic events of REM sleep, probably due to a generalized vasoconstriction seen in the skeletal muscles during phasic REM sleep.

Respiration. Different processes exist to maintain the regulation of respiration during sleep than during waking. Some

cells related to breathing stop firing during Slow Wave Sleep, some in REM. Overall, there is slight hypercapnia, a decrease in total ventilation, and a decreased sensitivity to inspired CO_2

During NREM there is a slight hypoventilation. This is due to a relaxation of upper airway muscles, as well as a decrease in the firing of inspiratory neurons, which show a decreased sensitivity to stimuli. Pco_2 levels raise while Po_2 levels fall. During NREM sleep, breathing is under chemical and mechanical feedback control.

During REM there is an overall higher and variable respiratory rate. It appears as though different processes maintain respiration during REM sleep, and it is not driven by vagal signals or peripheral or central chemoreceptors. It may be driven by higher cortical control, which may explain the variable rate. There is a lower tidal volume, and higher respiratory rate. As REM sleep is associated with a loss of muscle tone, there is an increase in the resistance of the upper airway. Obstructive sleep apnea can occur in certain individuals when the airway resistance increases to a degree which totally blocks ventilation.

Sleep Apnea is a lack of breathing (for at least 10 seconds) during sleep. This occurs at both ends of the age spectrum: it is seen in older patients, as well as in infants (SIDS). In adults, it is associated with daytime sleepiness and snoring. These patients are generally older, overweight males. SIDS (sudden infant death syndrome) is the leading cause of post-neonatal mortality. SIDS may be genetic and related to apnea in adults. Most deaths occur early in the morning, when SIDS babies have an increase in REM sleep and fewer awakenings. So there is a possibility that these infants have an increased arousal threshold, and don't awaken to increased Pco_2. An increased incidence of SIDS is seen with younger mothers, low birth weight, cocaine use and poverty, and there is the speculation that many of the cases may be due to parental neglect or abuse. However, there has been a sharp decrease in the incidence of SIDS in the last few years, when parents began to be advised to place their children on their backs for sleeping.

Renal. During sleep, urine production decreases, and the concentration of urine increases. There is a decrease in the glomerular filtration rate and the renal plasma flow. Secretion of aldosterone increases, as does ADH, both of which contribute to the decreased production of urine.

GI. The motility of the GI tract decreases during sleep. Gastric acid secretion also decreases during sleep, except in patients with duodenal ulcers, who show an increase of gastric acid secretion of 3-20 times normal levels during sleep. The swallowing reflex normally slows down during sleep, which helps explain the little puddle of drool left on your pillow.

Nervous System. Overall, there is a reduced discharge rate and brain metabolism during NREM sleep. During NREM sleep, there is an active inhibition of the reticular activating system. Neurons important in this inhibition are located in the basal forebrain (anterior hypothalamus and adjacent forebrain areas); lesions of the basal forebrain result in insomnia, while electrical stimulation causes an animal to enter into sleep. The thalamus, dorsal raphe, and nucleus tractus solitarius are also important in NREM sleep. During REM sleep, many parts of brain (visual cortex, limbic lobe) show increased firing rate and metabolism. Brain transection studies have shown that the pons is necessary and sufficient to generate the basic phenomena of REM sleep.

During NREM sleep, there is an increase in parasympathetic activity similar to relaxed wakefulness; sympathetic drives remain at about the same level as during relaxed wakefulness. During tonic REM sleep, parasympathetic activity remains about the same as during NREM sleep, but sympathetic activity decreases, resulting in an overall predominance of parasympathetic activity. However, during phasic REM sleep, both sympathetic and parasympathetic activity increase; sympathetic activation is generally favored.

Endocrinology. Stage 3,4 sleep is associated with increased secretion of Growth Hormone, especially in children approaching puberty. When your mother told you to get some sleep so you would grow up big and strong, she wasn't just necessarily telling you that so you would go to bed and give the poor woman a little peace; actually Mom was well versed in sleep physiology and was looking out for your continued hormonal health. Prolactin secretion is also tied to sleep; its secretion rises about 30-90 minutes after the onset of sleep. Sleep onset inhibits the release of cortisol.

Although it has become a very popular treatment for insomnia, the secretion of melatonin does not appear to be related to sleep cycles. Melatonin, which is synthesized in the pineal gland, is released at night, and is inhibited by light. While exogenous administration increases total sleep time and decreases sleep latency, its exact role in sleep is yet to be elucidated. At this point, there is no evidence that endogenous melatonin release is involved in sleep processes; it is thought that it may affect sleep by affecting circadian pacemaker or other factors *(i.e.,* body temperature) which indirectly affect sleep.

Thermoregulation. At sleep onset, the body temperature set point is lowered and body temperature falls. The body therefore employs heat loss mechanisms (sweating) to cool down the body to the new set point. Thermoregulatory cells in the preoptic/anterior hypothalamus slow firing during NREM sleep, only to stop firing entirely during REM sleep, when thermoregulation ceases.

THE NEUROCHEMISTRY OF SLEEP

Many drugs are commonly prescribed for the treatment of insomnia (Xanax, Valium, Dalmane, for example). Twenty five to thirty five percent of the American population (and up to 50 percent of elderly) report a problem with insomnia at some time. However, insomnia is "a symptom, not a disease; it is a perception by patients that their sleep is inadequate or abnormal."(3) Drugs don't address the problem, they just mask the symptom, as well as causing additional problems. Sleep results from the complex interaction of multiple neurotransmitter systems, as well as the influence of other physiological or psychological states. Since so many drugs that affect sleep are so widely prescribed, it is imperative that the pharmacy student develops a strong working knowledge of the neurochemistry of sleep.

The Neurochemistry of Wakefulness

Waking and consciousness depend on the activity, of neurons in the ascending reticular activating system of the brainstem. These neurons project into the thalamus, hypo-

thalamus and basal forebrain and eventually send projections to the cortex. There are particular neurotransmitters, such as the catecholamines, acetylcholine, histamine, glutamate and aspartate, that are localized within the reticular formation and have important roles in cortical activation and arousal.

The actions of some familiar drugs emphasize the neurochemistry of arousal and wakefulness. For instance, drugs such as cocaine and amphetamines increase levels of catecholamines. These drugs are important in pathways involved in behavioral arousal and cortical activation. These drugs decrease total sleep time, increase sleep latency, and decrease REM sleep. Amphetamines have therefore been used to treat the excessive sleepiness seen in Narcoleptics. Nicotine is another commonly used drug which increases arousal and vigilance. It acts on cholinergic receptors found in the reticular formation and the basal forebrain. These neurons are an important component of the ascending reticular activating system, and are thus involved in maintaining cortical activation and wakefulness(9). Anyone who's ever been knocked out by an antihistamine can appreciate the fact that histamine receptors in the caudal hypothalamus are involved in arousal mechanisms. Other excitatory neurotransmitters, such as glutamate and aspartate are involved in wakefulness. They are an important component of the ascending reticular activating system. Many other substances, such as CRF, TRF, TSH, ACTH and epinephrine are also important in maintaining wakefulness and cortical arousal.

The Neurochemistry of NREM Sleep

The anterior hypothalamus and adjacent forebrain areas are important in producing NREM sleep, as are the thalamus, dorsal raphe, and nucleus tractus solitarius. Neurotransmitters such as serotonin and GABA, which may be important in sleep mechanisms, are located in these brain regions and play an important role in sleep.

Serotonin (5-HT), found in raphe neurons of the brainstem, may be involved in sleep onset. Insomnia occurs when serotonergic cells of the dorsal raphe are lesioned. MAO Inhibitors (specific for 5-HT) enhance sleep. Also, there is evidence that substances in the biosynthetic pathway of serotonin (such as tryptophan and vitamin B6) may facilitate sleep(10). This is further evidence that your mother secretly studies sleep physiology: all that warm milk she tried to give you to help you sleep contained tryptophan. However, in spite of all the evidence supporting the role of serotonin in sleep onset, there are studies which suggest that the role of serotonin in sleep is not as clear cut as it may seem. The exact role of serotonin in sleep has not yet been elucidated.

The inhibitory neurotransmitter GABA is released in highest concentrations during NREM sleep. GABAergic neurons are located throughout the brain, including the basal forebrain, hypothalamus, thalamus, brainstem and cortex. Hypnotics, such as benzodiazepines (diazepam or triazolam) and barbiturates (phenobarbital, secobarbital) tend to work by potentiating GABA mediated inhibitory processes. Both bind to sites on GABA receptor complex, increase C1- flow through ionophore, causing hyperpolarizations and reduced cell firing. They may shut off neurons in the reticular activating system and inhibit transmission and activity of neurons that project to the cortex and thalamus. Overall, hypnotics do increase total sleep time, decrease sleep latency and decrease the number of awakenings. They also decrease the amount of time spent in NREM sleep stages 3,4 and, in some cases, REM sleep, which are sleep stages necessary for a normal, restorative night of sleep. Tolerance to these drugs develops fairly quickly (within two weeks) and insomnia and REM rebound are seen upon withdrawal from these drugs.

As evidenced by the veritable oceans of coffee it takes to maintain an average class of pharmacy students at peak efficiency, adenosine also plays a role in sleep. Caffeine blocks adenosine receptors; it is thought that adenosine may promote sleep. Intracerebroventricular infusion of adenosine will increase total sleep time in rats(9). Also, it is thought that benzodiazepines may in part exert their actions by blocking the reuptake of adenosine.

There are sleep inducing factors, which, when injected into the blood or cerebrospinal fluid of an animal, induce sleep. When one of these factors, Delta Sleep Inducing Peptide, was discovered by Monnier and his colleagues(11), there was much excitement in the sleep research community. However, there is probably not one single blood borne element that induces sleep, as conjoined twins do not fall asleep at the same time. Many other factors are also involved to varying degrees in sleep. Opiates, Somatostatin, Melanocyte Stimulating Hormone, Insulin, CCK, Prostaglandins, Growth Hormone and Prolactin may all play a role in sleep.

Neurochemistry of REM Sleep

Acetylcholine is located within neurons in the pontine tegmentum and is involved with REM sleep generation. " REM On cells" are cholinergic cells in the lateral pontine and medial medullary reticular areas that innervate the thalamus, hippocampus and hypothalamus. These cells discharge at high rates during REM and show little or no activity during NREM. Physostigmine, which inhibits catabolic enzymes, precipitates the appearance of REM sleep during NREM. The injection of carbachol, a muscarinic agonist, into the pontine tegmentum induces REM sleep. Blocking muscarinic receptors will retard the appearance of REM sleep.

Two symptoms associated with narcolepsy are cataplexy and hypnagogic hallucinations, whereby the patient loses all muscle tone and falls into a dream state while laying awake and paralyzed. Some have theorized that it is the sudden appearance of REM sleep into the waking state that causes these symptoms. Indeed, narcoleptic dogs are found to have increased levels of cholinergic receptors in their pons and medial medulla (12). Administration of cholinergic antagonists blocks these effects, which further illustrates the role of acetylcholine in REM sleep.

"REM Off cells" are noradrenergic and serotonergic cells found in the locus coeruleus and raphe. These are cells which are slow or silent during REM sleep. Affecting levels of norepinephirne or serotonin can have an effect on REM sleep. In general, antidepressants have the effect of decreasing REM sleep, which is elevated in human endogenous depression(13). Generally, the effectiveness of antidepressant drugs is proportional to the degree to which the drugs diminish REM sleep(14). Tricyclic antidepressants, such as amitryptyline and imipramine, block the reuptake of norepinephrine and serotonin, as well as having an anticholinergic effect. These drugs vary in their effectiveness as sedatives. The new generation antidepressants (*i.e.* Fluoxetine,

Sertraline) act specifically to block serotonin reuptake. Most of these drugs diminish REM sleep.

SUMMARY

An understanding of the basic mechanisms of sleep is important to anyone entering the health professions. Sleep is one of the most basic and important of human drives. In presenting the basics of sleep physiology, or the physiology of any process or organ system to pharmacy students, it is effective to stress the relevance of the subject to the students' every day lives, as well as the relevance to the practice of pharmacy. As many of the most frequently prescribed drugs have profound effects on sleep, the importance in understanding the basic mechanisms of sleep are easy to see

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