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Neurophysiology of Basic Molecules Affecting Sleep and Wakefulness Mechanisms, Fundamentals of Sleep Pharmacology

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Abstract

As part of the biological rhythm, the human brain has a healthy functioning with the ability to differentiate between day and night hours in any given day (sleep rhythm, life rhythm). From the control of hormone levels to muscle tonus, from the regulation of respiratory rate to the content of our thoughts, sleep has an impact on all bodily and cognitive functions. It is not surprising to see such effects of sleep on the body as it leads to significant changes in the electrical activity of the brain in general. Electrical signal changes in the brain (sleep-wakefulness rhythm) are regulated by neurohormonal molecules and their receptors in the body. Neurotransmitters that control sleep and wakefulness can be listed as “Glutamate, Acetylcholine, Histamine, Norepinephrine and GABA”. Main hormones are: Melatonin, Corticotropin Releasing Hormone (CRH), cortisol, prolactin, Growth Hormone (GH), Insulin like Growth Factor (IGF-1, Somatomedin-C), Follicle Stimulating Hormone (FSH) and Luteinizing Hormone (LH), progesterone, estrogen, testosterone, catecholamines, leptin and neuropeptide Y”. The effects of pharmacological agents on sleep and wakefulness cycles are materialized through the following molecules and their receptors: Hypnotics (GABA A agonists, benzodiazepines, gabapentin, tiagabine), sedative antidepressants (tricyclic antidepressants, trazadone, mirtazapine), antihistamines, medications used for the treatment of sleeplessness (melatonin and melatonin analogues), amphetamine (most commonly used stimulant), secretion of monoamines (dopamine), non-amphetamine stimulants used in the treatment of hypersomnia and narcolepsy (modafinil, bupropion, selegiline, caffeine) and other substances (alcohol, nicotine, anesthetics). To the extent we can conceptualize the physiological mechanisms of these basic molecules listed above and the regions they affect, we can appreciate the effects of these substances on sleep physiology and sleep disorders.

Keywords: sleep-wakefulness rhythm, major neurohormones, neurophysiological effects of sleep-wakefulness molecules, basic sleep pharmacology

1. Introduction

A healthy interaction between wakefulness and sleep periods and a balance specific to the organism is necessary for the proper functioning of human physiology and specifically that of the central nervous system (CNS) to be maintained. Sleep is a physiological need, it is a behavior during which the response of the brain to environmental stimuli is reversibly diminished. The absence or diminishment of this need negatively impacts the interactions in the neuronal networks and pathways responsible for the wakefulness of the brain. Electrical activity changes that appear in the brain during NREM and REM periods with the help of neurohumoral factors gives way to different physiological mechanisms in the body. Motor networks are integrated during REM, and non-motor ones during NREM. Thus, diseases that affect bodily organs and systems as well as medications can change NREM and REM activities thereby changing the motor and sensory functions of the brain. We can easily claim that many basic and clinical neurophysiological incidents taking place when we are awake are in fact realized through physiological processes and pathophysiological mechanisms occurring during sleep. Anxiety disorders, depression and schizophrenia where neurotransmitter-receptor relationships are hindered, as well as motor and non-motor degenerative diseases (Amyotrophic Lateral Sclerosis, Parkinson's disease) present with sleep disturbances and REM behavior changes years ahead of clinical symptoms. Sleep is as important a piece of life as wakefulness. As we continue to understand sleep, many of the causes of basic and clinical processes from pediatric age to geriatric years will be further demystified.

2. Neurophysiology of basic molecules affecting sleep and wakefulness mechanisms, fundamentals of sleep pharmacology

2.1 The relationship between behavior, limbic system and autonomous nervous system

When we talk about brain, we think about cortex; when cortex is mentioned, we focus on somatosensory (senses) and somatomotor (movement) cortex activities; when we hear about hypothalamus, we then consider hypothalamopituitary hormones and feedback mechanisms. Yet, humans are not limited to biological functions. Behavior is what defines a human being. Physiological and social characteristics associated with behaviors and even habits can influence the diseases individuals develop and the treatment approaches that are used. The emergence of behavior is managed by the limbic system which in itself means limit. Hypothalamus is at the center of the limbic system; rather than primarily focusing on biological-feedback interactions, it plays a key role in the integration and control of behavior [1–3]. The most important element of sleep and wakefulness cycle is our behavior model. Sleep is the most basic physiological need and the most important electrical activity of the brain influencing wakefulness behaviors (thirst, hunger, satiety, emotional state, mood, social motivation, love, compassion, argument, fear, attention, concentration, learning, memory and many other cognitive, motor, sensory and autonomous functions) [2–5]. Deep brain has hypothalamus at its center and it orchestrates affective sensations (like/dislike, satisfaction/revulsion, reward/punishment) together with surrounding limbic structures. As the main center of integration, hypothalamus uses parasympathetic and sympathetic fibers of the autonomous nervous system generating vegetative, emotional and motivational mechanisms. Amygdala is the main limbic structure for emotions: (1) it stimulates sympathetic activity, especially previously learned fear-related behavior. (2) Can be voluntary, when the cerebral

cortex decides to recall frightful experiences it acts through amygdala. (3) Some people can regulate some autonomic activities by gaining extraordinary control over their emotions. (4) It is sensitive to sleep deprivation that is why you get cranky when you have not slept enough. Reticular formation of brain stem, regulation of pupil size, respiration, heart, blood pressure, swallowing etc. Sleep/wakefulness cycle is a complex blend of all these physiological and behavioral processes. There are two distinct stages during sleep: a stage where there are no rapid eye movements NREM (Non Rapid Eye Movement) and one where there are rapid eye movements REM (Rapid Eye Movement). These stages are separated from one another and from wakefulness with hard limits [4–8].

2.2 Neuroanatomy of sleep and wakefulness behavior

There are two main regions (mesopontine reticular activating system (**RAS**) and **hypothalamus**; these two central regions modulate the intralaminar thalamus and neurons found in the basal forebrain) and a circadian pacemaker (**Suprachiasmatic Nucleus (SCN)**) with a central role that regulate the sleep and wakefulness cycle: **RAS** stimulates the cortex by ventral and dorsal tracts. Ventral tract stimulates the frontal parts of the brain through hypothalamus and subthalamus, dorsal tract stimulates it through the nucleus groups in the thalamus. During wakefulness, transmission of sensory information from thalamus is permitted through RAS control managed by thalamus. During sleep, the activity of RAS stops and the transmission of sensory information through thalamus is blocked and the stimulation of cortex is prevented. **Anatomic structures responsible for the hypothalamic control of sleep and wakefulness:** for wakefulness, stimuli originating from rostral pons and caudal midbrain regions reach paramedian midbrain in diencephalon and here, the signals divide into two paths aiming to reach thalamus and hypothalamus. Main structures projecting to thalamus are PedunculoPontine Tegmental (PPT) and LateroDorsal Tegmental (LDT) nuclei that are of cholinergic nature. The structure that initiates sleep is thought to be the ventrolateral preoptic nucleus (VLPO) located on the anterior part of the hypothalamus. VLPO suppresses the activities of brain stem, pons and locus coeruleus (LC), dorsal raphe nucleus (RN), laterodorsal tegmental pedunclopontine tegmental nucleus via GABA and galanine neurotransmitters. **Suprachiasmatic Nucleus (SCN)** is known as the light sensitive circadian pacemaker. During daytime, light stimulus is transmitted from retina to hypothalamus through neural pathways and it results in the secretion of melatonin from the pineal gland. It is an anatomical structure that has a central role in maintaining the day-night rhythm [1, 9–11]. It is multisynaptic and sympathetic nervous system contributes to this.

2.3 Physiology of neurotransmitters for sleep and wakefulness

2.3.1 Basic neurotransmitters for sleep and wakefulness cycle and a neurohormone

Dopamine: It is synthesized from L-Dopa with aromatic L-amino acid decarboxylase enzyme (cofactor pyridoxine). Dopamine receptors: D1 receptor; is found on nigrostriatal pathway specifically on nucleus caudatus, it plays a role on the initiation of locomotor system movements. D2 receptor; is found prominently in striatum and mesolimbic pathways, it plays a role in motor effects associated with extrapyramidal system. D3 receptor; is mostly found in the limbic system, it plays an important role in emotional and cognitive processes. D4 receptor; is increased in number in schizophrenia. D5 receptor; is important for the dopamine/acetylcholine balance in the basal ganglia and in maintaining a normal somatomotor and

striated muscle tone. Parkinson and Huntington chorea are prototypic diseases for decreased and increased dopaminergic activity, respectively. Dopamine decreases the secretions of prolactin and TRH [12–14].

Serotonin (5-hydroxytryptamine, 5-HT): L-Tryptophan is converted into 5-hydroxytryptamine (5-HT) with tryptophan hydroxylase (5-hydroxytryptophane) and amino acid decarboxylase enzymes. Most of the serotonergic pathways are found within the Raphe system (2 pathways) in the brain. **(1) Ascending pathway:** Regulation of feeding behavior (decreases the appetite together with histamine and nicotine), continuation of normal behavioral patterns, regulation of NREM-REM sleep cycle, hormonal regulation (increases ACTH and prolactin secretions, decreases GnRH secretion), depression, anxiety and migraine pathogenesis. **(2) Descending pathway:** Acts as a modulator in the transmission of pain sensation to the central level. Serotonin receptors: 5HT1-A: Shows an anxiolytic effect. 5HT1-B: It is a presynaptic inhibitor. 5HT1-D: Closes the AV shunts in the brain, plays a role in migraine pathogenesis. 5HT2: Has excitatory effects on behavior. 5HT2-C: Specifically found in choroid plexus where atypical antipsychotic clozapine exerts its effects. 5HT3: Stimulates the respiratory center and is found in the autonomous nervous system. 5HT4: Primarily found in the myenteric plexus within the gastrointestinal system [12–14].

Adenosine: It is a nucleoside naturally found in all bodily cells. It forms molecules like adenosine triphosphate (ATP) and adenosine diphosphate (ADP) to transmit energy inside the cells; at the same time, it is one of the chemical messengers (xanthine) or neurotransmitters in the brain. It is a substance that is produced either directly or as a result of ATP hydrolysis. It is broken down by adenosine deaminase. It has 2 known receptors: P1 (A1–4) and (A1 and A2 receptors are blocked by methyl xanthines) P2X-2Y. It has depressant effects on the CNS. As an inhibitor transmitter in the brain, it shows an incremental increase specifically in RAS throughout the wakefulness period; when it reaches its highest level, adenosine inhibition takes place, sleep starts and adenosine concentration gradually decreases during sleep. Caffeine blocks the depressant effects of adenosine on the brain, decreases adenosine inhibition and provides for the continuation of wakefulness while carbamazepine (adenosine agonist, antiepileptic) helps to continue adenosine inhibition [15–17].

Melatonin (A neurohormone that identifies daytime and nighttime): It plays an important role in identifying the circadian rhythm. It is synthesized from 5-HT in the pineal gland by acetyltransferase and methyltransferase enzymes. Melatonin receptors are mostly found in SCN. The physiological actions of melatonin are mediated by two G-protein coupled membrane receptors, which belong to the family of the quinone reductases. Melatonin receptors: MT1; is primarily found in the human skin. It is associated with the aging process and Alzheimer's disease. MT1 and MT2 receptors are expressed in the SCN and they have distinct functional roles in sleep regulation. Activation of the MT1 receptor suppresses neuronal firing rates in the SCN, while MT2 mainly acts by inducing circadian rhythm phase shifts. MT2; has anxiolytic, antidepressant and hypnotic effects and is related to pain pathophysiology. MT3; is related to quinone reductase enzyme and it plays a role in the prevention of stress as well as detoxification [18–20].

2.3.2 Neurotransmitters in charge of sleep and wakefulness

“Glutamate, Acetylcholine, Histamine, Norepinephrine and GABA”

Glutamate: It is the main excitatory neurotransmitter in the brain and medulla spinalis. Its inactive form is glutamine. It plays a primary role in the generation of

excitatory postsynaptic potentials and long-term potentiation in the brain and these are the most important mechanisms in learning and memory formation. Its most important receptors are: NMDA (N-methyl-D-aspartate; it is a Na^+ - K^+ - Ca^{++} channel type receptor, its selective antagonist is phencyclidine and its endogenous blocker is Mg^{++}), AMPA (alpha-amino-3-hydroxy-5 methyl-4- isoxazole propionic acid), Kainate (kainic acid) receptors (KARs) [12–13].

Acetylcholine: It has muscarinic and nicotinic receptors in the CNS. Nearly 80% of the cholinergic pathways in the brain originate from Meynert's nucleus basalis. Nicotinic receptors are mainly found in Renshaw cells that inhibit alpha motor neurons in medulla spinalis. In addition to learning and memory functions, they also play a role in the balanced functioning of the extrapyramidal system. A parallelism has been shown between the degeneration of this pathway and the occurrence of Alzheimer's disease and Huntington chorea [12–14].

Histamine: Ventral posterior hypothalamus and tuberomammillary nucleus (TMN) receiving histaminergic projections have the highest concentrations of histaminergic neurons in the brain. H1 receptors are found in glial cells and H3 receptors are in basal ganglia. Serotonin-like effects of histamine are: (1) to decrease the appetite and (2) to increase the secretion of ACTH and prolactin [13, 14].

Norepinephrine: In the CNS, catecholaminergic neurons are most abundant in locus coeruleus. The highest concentrations of norepinephrine are found in hypothalamus, nucleus amygdala and the dentate gyrus of hippocampus. Medullar reticular formation harbors the highest levels of epinephrine. It has Beta 1 and 2 activator receptors which are widespread in the CNS. Alpha 1 causes vigilance (behavioral activations). Alpha 2 acts as an autoreceptor at presynaptic level and is inhibitory in nature (sedation). The activation of this system in the CNS leads to panic reaction presenting with alertness, fear and a state of alarm. Furthermore, it causes anxiety and tremor. However, the decrease in the efficacy of this system leads to depression. Catecholamines also increase the secretions of GnRH and ACTH [12–14].

Gamma-Aminobutyric Acid (GABA): It is the main inhibitory mediator of the brain. GABA is synthesized from glutamic acid by glutamic acid decarboxylase enzyme (activated by valproic acid). The main route of its inactivation in the synaptic space is re-uptake and it is broken into succinic acid semialdehyde by the GABA transaminase enzyme (inhibited by vigabatrin). It has two receptors of inhibitory character: (1) GABA-A receptor is a chlorine channel. When it is activated, due to the influx of the Cl ions, intracellular negativity increases (hyperpolarization). This receptor has 5 subunits (2 alpha, 2 beta, 1 gamma): The agonist for the beta subunit is muscimol, its antagonist is bicuculline; alpha subunit is a benzodiazepine receptor. Barbiturate is a Cl channel agonist, while picrotoxin and pentylenetetrazole are antagonists. It has binding regions for ethanol and ivermectin. (2) GABA-B receptor is not of ion channel character. It is not affected by benzodiazepines or barbiturates. It is activated by baclofen and antagonized by flaclofen and saclofen [14–16].

2.3.3 Mechanism of action of neurotransmitters on sleep and wakefulness neurons

Reticular activating system stimulates the cortex by utilizing glutamate while ponto-mesencephalic tegmental neurons do this by using acetylcholine. Neurons at locus coeruleus predominantly utilize norepinephrine, they extend from the brain stem to the cerebral cortex encompassing the forebrain; by activating the stimulation of the cortex, and they contribute to maintaining wakefulness. **Cholinergic neuronal network** leads to wakefulness in two types of cortexes:

1. It projects to laterodorsal tegmental and pedunculopontine tegmental nuclei, midline and intralaminar thalamic nuclei and to a lesser degree to lateral hypothalamus and basal forebrain.
2. Cholinergic neuron group starts from the basal forebrain with a widespread projection to cortex. This pontomesencephalic neuron group is a part of the ascending reticular activating system; they play a part in the activation during wakefulness and are actively involved in paradoxical sleep. Glutamate is another excitatory neurotransmitter acting as the primary neurotransmitter of the ascending reticular activating system. **Glutamate** is found at very high concentrations at the brainstem reticular formation. It plays an active role in the wakeful brain and is secreted from the cortical cells during wakefulness. During deep sleep, slow wave sleep (SWS) “burst discharges” appear as a result of the activation of special glutamate receptors. Histamine plays an important role in wakefulness as well. **Histamine containing neurons** are found in tuberomammillary nuclei and posterior hypothalamus. **Noradrenergic neurons** (locus coeruleus), have diffuse projections in the brain extending to the cortex. Histaminergic neurons are associated with cortical activation during wakefulness while they are shut down during REM sleep. Sleep requires a shift from sympathetic regulation to parasympathetic regulation. Parasympathetic centers of significance are located in “solitary tract nucleus neurons, anterior hypothalamus and preoptic fields”. When increasing **adenosine** concentrations in RAS reach their highest levels, **serotonergic raphe neurons** facilitate the beginning of sleep while **GABA-ergic neurons** inhibit the activating system. These GABA-ergic neurons are selectively activated during SWS. As a result of this inhibition, brain stem, hypothalamus and nasal forebrain are suppressed and disfacilitation (inhibition) and hyperpolarization of thalamocortical system takes place. Thereby, from the wakeful state where we see rapid, tonic discharges on EEG, the system shifts into sleep state where we start recording sleep spindles and slow wave activity. Initiation and continuation of SWS is made possible by lengthening and strengthening the inhibition of the activating system with GABA-ergic system. Metabolic rate of adenosine dictates sensitivity to sleep deprivation while directly influencing the quality and duration of SWS [6, 9, 20–25].

2.3.4 The physiology of the circadian system and melatonin in the regulation of circadian rhythm

In Latin, circa means pertaining to and dian means day; circadian is a word used to explain the daily physiological rhythms of an organism, mainly the sleep and wakefulness.

The anatomy of the circadian rhythm: The regions in charge of the circadian rhythm in mammals are the right and the left suprachiasmatic nuclei (SCN) located in the anterior hypothalamus. SCN is divided into ventrolateral and dorsomedial sections on the basis of biochemical structure, peptide phenotypes and afferent-efferent pathways. SCN is affected by environmental changes such as light and time of nutrition. SCN also has functional regions that regulate circadian rhythm outputs associated with neural activity. Light is perceived by retinal photoreceptors (cones, rods, retinal ganglion cells containing melanopsin). The action potentials that are generated here lead to the secretion of glutamate and pituitary adenylate cyclase activating polypeptide via retinohypothalamic pathways. Information about light intensity and temporal stimulus is directly transmitted to SNC while it is indirectly transferred to the lateral geniculate region

in the thalamus. SCN receives significant inputs from serotonergic median raphe nucleus and intergeniculate region containing neuropeptide Y and GABA (These regions are not essential for circadian rhythm; however, they transfer information about light sensitive phase changes and stimulants other than light to the circadian rhythm center). The effects of light on SCN activity and circadian phase changes are completely opposite of those of neuropeptide Y and serotonin. As the center of circadian rhythm, SCN contributes to the regulation of behavioral, physiological and genetic rhythms. The most important aspect is its relationship with hypothalamus; (1) Main neuronal pathway regulating sleep-wakefulness rhythm SCN – neighboring supraventricular region, SCN-dorsomedial hypothalamic region (2) SCN-sends both direct and indirect fibers to paraventricular hypothalamic nucleus regulating corticosteroid secretion and melatonin synthesis. The regulation of the circadian rhythm improves the adaptation of the organism to life; towards the end of a night's sleep, body temperature, plasma cortisol levels and sympathetic autonomous activity all increase. When sleep time approaches, body temperature decreases and melatonin secretion starts. In mammals, circadian rhythm center at SCN regulates the phases and timings of all cyclical behavioral functions together with sleep-wakefulness cycle. Identifying the neuronal pathways and neurotransmitters playing a role in this regulation is crucial for developing pharmacological and strategical approaches for chronobiological sleep disorders [25–27].

Melatonin in the regulation of sleep and circadian rhythm: Melatonin is the neuroendocrine modulator of day-night rhythm with receptors densely located at the suprachiasmatic nucleus (SCN). The endogenous circadian rhythm of melatonin secretion is directly proportional to the endogenous rhythm of sleep tendency. Secretion of melatonin from the pineal gland is controlled by SCN. This pathway is multisynaptic and has contributions from the sympathetic nervous system. When administered to the body from outside melatonin helps initiate sleep; as it leads to phase shifts, it has therapeutic effects in insomnia and regulation of sleep-wakefulness phases. The biological clock can be regarded as an insurance preventing sleep phase shifts caused by homeostatic changes. When human beings intend to change the timing of sleep-wakefulness rhythms at their own will (most common causes are travels to regions with time differences and working with shifts), insomnia ensues.

Sleep regulation, Homeostasis, Sleep homeostasis and Sleep-wakefulness rhythm: Three main processes play a role in sleep regulation: (1) Homeostatic process which tells us the relationship between the last sleep and wakefulness periods. In sleep deprived organisms the duration and depth of sleep increases as a compensatory mechanism. (2) Circadian process; in other words the biological clock. (3) Ultradian process which defines the duration of REM—NREM sleep cycles and the interactions between them. Sleep wakefulness rhythm is identified by circadian and homeostatic processes. Homeostasis is the preservation of required internal environment conditions (extracellular fluid) for maintaining the vitality of the organism. Sleep homeostasis is the equivalent of sleep-wakefulness balance in sleep regulation. This balance is maintained by homeostatic mechanisms and deviations from the normal are either normalized or brought closer to normal. Circadian process can be regarded as an internal clock that lasts 24 hours. Homeostatic process is related to the time spent awake before sleeping. Therefore, there are three important features of a medication to be used in the treatment of insomnia caused by circadian clock changes: (1) Hypnotic effect: the ability to initiate or to maintain sleep when homeostatic effect is inadequate to do so. (2) Chronohypnotic effect: the ability to inhibit the time of waking-up normally regulated by the circadian center. (3) Chronobiotic effect: concerning the regulation of the circadian rhythm, the ability to initiate phase shifts and to do so during desired hours. **Melatonin** is a hormone that harbors all these three features.

Secretion of melatonin from the pineal gland is controlled by SCN. Furthermore, it is multisynaptic and has contributions from the CNS. If there is light exposure during night hours, melatonin levels decrease immediately. Melatonin levels are influenced by certain medications: Beta blockers used for the prophylaxis of hypertension, cardiac arrhythmias and headaches block the sympathetic activity both at the heart and at the pineal gland. On the other hand, antidepressant drug fluvoxamine prevents the degradation of melatonin and increases its plasma concentrations. Administration of 0.3–80 mg oral melatonin during daytime when endogenous melatonin levels are low, will decrease sleep latency and have a sleep inducing effect. Melatonin effect is related to body posture; it increases when lying down and decreases when standing up. Neurotransmitter imbalance is present in SCN of essential hypertension patients and there is a decrease in the secretion of melatonin in coronary artery disease that follows. In patients with uncontrolled hypertension, taking 2.5 mg of melatonin 1 hour before sleep is shown to increase the total duration and the efficacy of sleep. **EEG pattern of sleep regulation:** Sleep regulation is mainly identified by sleep homeostasis: in sleep deprivation, the length of sleep increases and it gets deeper as a compensatory mechanism. Because sleep needs are identified by the homeostatic and circadian processes. As the time spent awake before sleeping increases, slow waves in sleep EEG increase and sleep spindles decrease. Neurophysiologically, thalamocortical neurons have a moderate level hyperpolarization during the superficial stages of NREM sleep (N1 and N2) and high level of polarization during deep stages (N3) of NREM. During superficial NREM sleep, there are more frequent thalamocortical discharges and EEG equivalent of these are sleep spindles. Theta activity in awake EEG shows the homeostatic process. As the period spent awake gets longer, theta activity increases and SWS (delta) activity increases to the same extent. Despite the fact that their mechanisms of action are different, similar to benzodiazepines the use of melatonin suppresses low frequency EEG activity [27–29].

2.4 The effects of sleep and circadian rhythm on hormones

Circadian rhythmicity and sleep-wakefulness homeostasis includes; (1) the modulation of hypothalamic hormones, peptides and molecules, (2) the metabolic pathways influenced by peripheral hormones and (3) autonomous nervous system control of endocrine organs. In the regulation of temporal organization of hormone secretion, processes associated with the electrical signal changes during the sleep stages of brain (NREM-REM) are as effective as circadian rhythm and homeostatic processes. These processes effect different hormonal axes (somatotrophic, corticotrophic and gonadal axes) and metabolic pathways at different levels. For example thyroid stimulating hormone (TSH) levels might change both with sleep and circadian rhythm while cortisol levels only change with circadian rhythm. Growth hormone (GH) and prolactin (PRL) can be at a certain level during daytime- wakefulness but they increase while sleeping. Glucose and insulin have been shown to be effected by both sleep and the circadian rhythm increasing while being awake at night and while being asleep during daytime. Circadian oscillations can be generated in many peripheral organs under autonomous nervous system control including adipocytes and pancreas beta cells that generate endocrine signals. These “local” oscillators seem to be under the control of central electrical batteries found in suprachiasmatic nuclei either directly through neural and endocrine signals or indirectly via sleep-wakefulness cycle and behavioral rhythms like nutrition. Endocrine secretion of these peripheral oscillators during wakefulness and sleep and their possible participation in the temporal organization of metabolic function are still open to research [30–32].

2.4.1 Somatotropic axis and sleep

Growth Hormone (GH): Pituitary secretion of GH is stimulated by hypothalamic GH secreting hormone (GHRH) and is inhibited by somatostatin. Acylated form of ghrelin that is predominantly produced in the stomach binds to growth hormone secreting (GHS) receptors and endogenously stimulates GH secretion. GH is a respiratory stimulant. Animal studies have shown that the infusions of GHRH and ghrelin result in SWS, while GH infusion leads to REM sleep. There is a consistent relationship between the presence of Delta waves on EEG and high concentrations of GH and maximum GH secretion takes place minutes after the start of SWS. Pharmacological agents used in narcolepsy like gamma hydroxyl butyrate (GHB) and ritanserin that stimulate SWS cause an increase in GH. Sleep-initiated GH secretion is regulated by GHRH stimulation that primarily takes place during somatotropin inhibition where somatotropic activity decreases. Secretion of GH during early sleep is suppressed by the administration of a GHRH antagonist [15]. SWS decreases with age and there are also medical conditions that result in sleep fragmentation which all decrease GH secretion. Sleep deprivation effects GH secretion through deteriorations in both the circadian rhythm and sleep-wakefulness homeostasis. **Insulin like Growth Factor (IGF-1) (Somatomedin C):** It is a hormone primarily synthesized in the liver by being stimulated with GH. It mediates the anabolizing effects of GH in the muscle tissue. In men it decreased after 21 years of age while there is a rapid decline in women after menopause. It is a respiratory stimulant like GH and leads to increases in SWS. **Somatostatin:** Inhibits the GHRH stimulation of GH secretion. It has a suppressive effect on the respiratory center and is thought to play a role in sudden infant death syndrome [33–35].

2.4.2 Corticotropic axis and sleep

The activity of the corticotropic axis is related to stress reaction and behavioral activation. Corticotropic axis activity can be measured peripherally by plasma levels of pituitary adrenocorticotrophic hormone (ACTH) and adrenal hormone cortisol that is directly controlled by ACTH stimulation. Plasma levels of these hormones are highest during early hours of morning, they decrease throughout the day reaching lowest limit during late night hours and early stages of sleep period. Therefore, sleep is normally initiated when corticotropic activity is slow. Reactivation of ACTH and cortisol secretion happens suddenly a couple of hours ahead of waking up.

Corticotropin releasing hormone (CRH): It regulates GnRH secretion and stimulates adrenocorticotrophic hormone secretion (ACTH) from the pituitary gland. It binds to CRH receptors that are abundant in the brain and stimulates breathing. In instances of stress it acts as a part of hypothalamo pituitary adrenal axis and increases plasma cortisol levels. **Cortisol:** Physiologically low levels of cortisol at the beginning of sleep is correlated with SWS and cortisol secretion mostly starts during superficial stages of sleep. When there is sleep deprivation, cortisol levels act in parallel to circadian rhythm increasing and decreasing at the same time; however, as there is a change in the time sleep starts and ends, cortisol levels are somewhat higher during nighttime (where it should be lower), and somewhat lower during the day (where it should be higher) (thus the amplitude of cortisol rhythm decreases). In elderly individuals with fragmented sleep and decreased SWS, worsened memory and insulin resistance that is observed is related to the increased cortisol levels at night. Waking up during fragmented sleep results in increases in cortisone levels (as concerns cortisol increase and sleep fragmentation, it is not clear which one is the cause and which is the result). Cushing patients were shown to have bad sleep quality, decreases in REM latency, increases in first REM

intensity and decreases in deep sleep. Addison patients also had decreases in deep sleep. Therefore, we can conclude that for deep sleep to happen, the organism needs cortisol rhythm within normal limits [36–38].

2.4.3 Thyrotropic axis and sleep

Thyroid Stimulating Hormone (TSH)-Triiodothyronine (T3)-Thyroxine (T4): It is stable throughout the day and increases during the early hours of the evening reaching its maximum level at the beginning of sleep. Before waking up in the morning, it returns to its stable levels that continue through the day. TSH secretion is influenced by the circadian rhythm and by sleep. Sleep had an inhibitory effect on TSH. This effect disappears during sleep deprivation, nocturnal TSH levels increase together with increases in T3 and T4. Thyroid hormones are respiratory stimulants. In hypothyroidism, there is a tendency for hypoventilation and obstructive apnea syndrome. There is sleepiness during daytime and decreases in SWS. In hyperthyroidism, there is increased movement during sleep, decreased REM duration and insomnia due to increased metabolic rate [39, 40].

2.4.4 Prolactin (PRL) and sleep

PRL levels begin to increase shortly after the start of sleep and make a night peak at the middle of sleep. The possible primary mechanism underlying this peak is decreased dopaminergic inhibition of PRL during sleep. Thyrotropin releasing hormone (TRH), vasoactive intestinal peptide (VIP), oxytocin, estrogen and angiotensin II increase PRL secretion while dopamine, GABA and acute hypoxia inhibits it. The primary effect of PRL during sleep is to stimulate REM sleep. Rapid PRL increase at the beginning of sleep is thought to be related to SWS. In prolactinoma and lactating mothers SWS increases due to increased PRL secretion. Fragmented sleep decreases PRL secretion (Mechanism: Waking up in the morning and wakefulness that fragment sleep are related to a rapid inhibition of PRL secretion) [41, 42].

2.4.5 Gonadal axis and sleep

The relationship between 24-hour-gonadotropin secretion rhythms and gonadal steroid levels changes based on the stage of maturity and is sex-related during young adulthood [42].

Gonadotropins: Before puberty, luteinizing hormone (LH) and follicle stimulating hormone (FSH), is secreted in a pulsatile fashion both in boys and girls. Increased amplitude of gonadotropin secretion during sleep is a distinctive characteristic of adolescence. In adolescent girls, estradiol levels are higher during the day than the night; in adolescent boys high levels of testosterone during nighttime coincide with increases in gonadotropins. Both sleep and circadian rhythm contribute to the increases in gonadotropin pulsations during the night in adolescents. As they transition into adulthood, the effect of circadian rhythm either decreases or disappears completely. In sleep deprivation, LH increases, FSH does not change. Adult 24-hour plasma LH levels are regulated by the menstrual cycle in women, in men it changes according to NREM-REM cycles. In young men, REM sleep deprivation weakens night increases of testosterone in particular. In elderly men, there is a decrease in LH secretion during sleep while it increases in elderly women; however this is not in relation with the circadian rhythm. **Progesterone:** It increases during pregnancy and during the luteal phase of menstrual cycle. As it is a respiratory stimulant, there are low carbon dioxide levels and hyperventilation during these periods. When progesterone decreases during the postmenopausal period,

nocturnal desaturation, hypopnea and apneas are seen more frequently. In individuals administered with estrogen and progesterone during postmenopausal period, sleep breathing disorders were less common. **Estrogen:** In young women, it is at its lowest level during menstruation and at its highest during the midluteal phase (estradiol). It is in the form of estrone during postmenopause. Estradiol increases the effects of progesterone on respiration by increasing the number of progesterone receptors. **Testosterone:** Despite the low amplitude of nighttime increase in gonadotropin secretion, there is a significant diurnal rhythm for testosterone levels in the circulation. Testosterone is at its lowest levels during the late hours of the night; after sleep starts, there is a strong increase and it reaches its maximum levels during the early hours of the morning [51, 52]. Therefore, the strong circadian rhythm of plasma testosterone can be partially controlled by factors other than LH. Nighttime increase of testosterone is temporarily related to the delay of first REM episode. There are studies showing that sleep breathing problems are due to decreased levels of testosterone during nighttime as well as those showing that respiratory stimulation is decreased by the negative effect on progesterone [43–46].

2.4.6 Catecholaminergic axis and sleep

With initiation of sleep, noradrenaline and adrenaline levels decrease as the case with cortisol reaching their minimum levels within an hour. Noradrenaline plays a role in respiratory control while adrenaline is a bronchodilator. Nocturnal catecholamine levels are increased in patients with obstructive apnea syndrome.

2.5 Physiological mechanisms of basic molecules that cause sleep related metabolic changes

2.5.1 Molecules mediating nutrition and sleep regulation

Sleep plays an important role in energy balance. Hypocretins and orexins are hypothalamic stimulant neuropeptides with strong wakefulness promoting effects, they also stimulate feeding; their definition created the molecular basis for delineating the interactions between nutrition and sleep regulation.

Orexin: Orexin containing neurons in lateral hypothalamus directly lead to locus coeruleus and other brainstem and hypothalamic stimulation areas; here they interact with leptin sensitive neuronal network which plays a role in balancing food intake and energy consumption. Orexin containing neurons are active when awake and inactive when asleep. Orexin activity is inhibited by leptin which is a satiety hormone and stimulated by ghrelin, an appetite stimulating hormone. **Leptin:** Leptin is a hormone secreted by adipocytes, it provides information to the regulating centers at hypothalamus about energy status. Nighttime increases of leptin is thought to suppress hunger during night fasting. When administered systemically, it causes increases in SWS and decreases in REM. As it inhibits Neuropeptide Y (suppresses respiration) secretion, it stimulates corticotropin releasing hormone-CRH (stimulates respiration) secretion. Research trials have shown that it stimulated respiration and that CPAP (continuous positive air pressure) treatment decreased leptin receptor sensitivity. Long term total sleep deprivation decreases leptin levels. **Ghrelin:** It plays a role in regulating energy balance and stimulating appetite. Ghrelin levels increase sharply before each fixed meal time and make a nadir 1–2 hours after eating. Although hunger continues, ghrelin levels do not continue to increase throughout sleep and decreases during later hours of sleep instead. When at high levels during sleep, it is a strong endogenous stimulant of GH secretion [43, 47–49]. **Neuropeptide Y (NPY):** NPY is widely distributed

in hypothalamus, amygdala, locus coeruleus and cerebral cortex. At least six NPY receptor subtypes have been defined. NPY plays a role in food intake, hormonal secretion, circadian rhythms, stress reaction, anxiety and sleep functions. In animals, depending on the site of injection, NPY was found to have sleep promoting effects as well as wakefulness effects. In humans, NPY is thought to have hypnotic characteristics and act as a physiological antagonist of CRH. NPY participates in the timing of sleep onset in humans and can thus play a role in the integration of sleep regulation, food intake and metabolism [43, 50].

2.5.2 Autonomic nervous system co-transmitters (neuropeptides)

Nuclei located in hypothalamus (posterior and lateral regions contain sympathetic nuclei, anterior regions have parasympathetic ones) control the autonomic nervous system. Together with hypothalamus and limbic structures, sympathetic and parasympathetic portions of the autonomic nervous system regulate vegetative sensory and motivational behaviors. Norepinephrine (noradrenaline) is the main transmitter for the sympathetic system (catecholaminergic system), and Neuropeptide Y acts as a cotransmitter. In vascular beds, adrenergic endings secrete NPY together with noradrenaline. By itself, NPY has a vasoconstrictor effect. Acetylcholine (ACh) is the main transmitter of the parasympathetic system (cholinergic system) and VIP (vasoactive intestinal peptide) functions as the cotransmitter of this system. In the salivary and perspiratory glands, in the genital system and adrenal medulla cholinergic endings secrete VIP together with ACh. VIP exerts partial vasodilator and strong bronchodilator effects [7, 12–14].

2.5.3 Melanin-concentrating hormone (MCH)

MCH, is a 19 amino acid long cyclic neuropeptide acting as a neurotransmitter. Neurons containing MCH are primarily found in lateral hypothalamus and incerto-hypothalamic regions and they have widespread projections within the brain. In humans, biological functions of this neuropeptide are realized via two metabotropic receptors, namely MCHR1 and MCHR2, whereas rodents only have MCHR1. **General functions in the organism:** (1) Feeding behavior and energy conservation; high concentrations of MCH, might lead to increased eating and is associated with increases in body mass. On the contrary, decreases in existing levels of MCH can lead to decreased eating. Increased MCH levels in olfactory regions have been associated with the consumption of oily foods with high calorie content. Good tasting food items promote MCH encouraging higher consumption of them. Sugar, specifically glucose seems to be supporting the role of MCH in sleep and energy conservation. Supporting energy conservation in this manner has been associated with high body mass even when the diet is under control. (2) Having MCH at certain locations only during lactation seems to help promote maternal behavior. (3) Reproduction: MCH has been assumed to act as a modulator in Luteinizing Hormone (LH) secretion by having a direct effect on the pituitary gland or by indirectly influencing gonadotropin releasing hormone (GNRH) in the hypothalamus. Estrogen seems to be required for MCH to influence reproduction. (4) Skin pigmentation: MCHR1 has been found in human melanocytes and certain melanoma cells. In these cells, it has an antagonistic relationship with α -MSH and it decreases melanin production. **Specific regulation of sleep behavior:** As concerns the sleep cycle, MCH and orexin have an antagonistic relationship with one another, orexin is nearly totally active during wakefulness periods and MCH is more active. MCHergic neurons are more active during sleep, specifically during REM sleep; although they increase SWS as well, they mainly increase the duration of REM sleep. MCH

knockout mice have shorter REM sleep especially under negative energy balance circumstances. Systemically administered MCHR1 antagonists decrease sleep. While MCH promotes sleep, there are limited number of studies associating MCH with narcolepsy. Narcolepsy has long been described as a disorder of REM sleep mechanism. An individual with narcolepsy starts sleeping with REM sleep. Narcolepsy presents with the loss of hypothalamic cells that contain hypocretin and orexin. A research study has demonstrated that individuals having narcolepsy had diminished orexin neurons that would promote wakefulness and that the number of MCH neurons was not different than those of an average individual who does not have narcolepsy. MCH has been associated with depression and anxiety. MCHR1 antagonists were shown to act as antidepressants [1]. Chemokines and cytokines generally appear as a result of inflammation or infection and can then damage MCH neurons thereby possibly causing anorexia in an individual. MCH has been identified both in melanoma and squamous cell carcinoma cell lines [43, 51–54].

2.6 Overview (a general look at sleep related neuropharmacology)

The system and molecules that are in charge of regulating sleep-wakefulness modulate general homeostatic mechanisms as well as orchestrating highly cognitive activities like attention, learning and memory. We need to develop a general perspective for pharmacologic substances influencing these activities.

2.6.1 Alcohol

Ethyl alcohol; blocks glutamate NMDA receptors and is an indirect agonist of GABA receptors. Cerebral granular cells increase GABAergic transmission in cerebellar cortex and hippocampus. Alcohol is neurotoxic at high doses; it can specifically hinder cholinergic input that advances to the cortex through basal forebrain neurons. It can lead to a significant deterioration in motor performance and can result in sleep deprivation. There might be behavioral problems stemming from sleep deficiency as well as memory problems in alcoholics because of apparent effects of alcohol on hippocampus. Individuals having undiagnosed schizophrenia, anxiety disorders and depression might try to benefit from sedative and anxiolytic effects of alcohol by overconsumption. In these individuals, blood circulation to the frontal region deteriorates and their decision making capacity is impaired [14, 15].

2.6.2 Anesthetics, sedatives and hypnotics

Main mechanisms of effect for sleep inducing pharmacological agents are still being delineated. The primary site of action of most anesthetics may be the sleep-wake control system. In anesthesia, considering that arousal and alertness represent a continuum of levels from mania to coma, with physiological and behavioral concomitants, the monitoring of EEG, along with behavioral and autonomic signs, should be used routinely to assess level of anesthesia. **Most anesthetics**, including barbiturates, etomidate, propofol, neuroactive steroids, and volatile anesthetics, act on GABA_A receptors among other receptors. Sedation and natural sleep occur greatly as a result of enhanced GABAergic transmission, which in turn affects the release of a number of excitatory transmitters such as acetylcholine, excitatory amino acids, and histamine. Actions may take place specifically in such regions as the RAS, TMN, and basal forebrain (all of which have local circuit GABAergic neurons and receive GABAergic input from VLPO, as described earlier), thereby regulating the level of arousal. The benzodiazepines act by binding to a site that modulates GABA receptors, especially GABA_A receptors. These agents produce

sedative, hypnotic, anxiolytic, and anticonvulsant activities. They act generally by amplifying GABAergic transmission, such that short-acting agents have been used to promote sleep in insomnia patients, although more recently, effective non-benzodiazepine hypnotics have been developed. These agents also act to facilitate GABA_A receptor function (e.g., zolpidem and zaleplon). Insomnia is a very common symptom, especially in the elderly, and has a number of causes, including physical, social, and psychiatric. **Antidepressants with sedative effects (tricyclic antidepressants, trazadone, nefazadone and mirtazapine)** exert their effects on emotional state via 5-HT norepinephrine (NE) receptors, their sedative effects are seen through H₁, 5-HT₂, α ₁ receptor antagonisms. **Drugs used in insomnia treatment** (melatonin and melatonin analogues) exert their effects via MT₁ and MT₂ receptors. **Other hypnotic substances acting through GABA** (Valerian preparations, Gabapentin, Tiagabine), **Sedative antipsychotics** (Olanzapine, quetiapine; they are 5HT-2A antagonists), **Gamma hydroxybutyrate** (its mechanism of effect is not fully understood, it is considered to modulate dopamine activity; it is recommended in narcolepsy for cataplexy treatment) [14, 15, 55, 56].

2.6.3 Antihistamines

Histaminergic projections at tuberomammillary nucleus are active during waking up. The pathology of this region leads to hypersomnia. Histaminergic inputs coming from TMN to RAS suppress SWS, but they do not have an effect on REM. RAS, basal forebrain, lateral hypothalamus and cortex have high levels of histamine receptors. Antihistamine (histamine receptor blockers) effects on these regions cause dizziness, sleepiness and cognitive dysfunction. In children first and second generation antihistamines can cause poisoning and coma; however, newer (third generation) pediatric formulations (e.g. fexofenadine, loratadine, cetirizine) seem to be safer [57].

2.6.4 Caffeine

The popularity of caffeine is due to its stimulant characteristics. It blocks adenosine receptors in RAS, decreases the inhibitor effect of adenosine; thus, free adenosine levels in the brain are increased resulting in a stimulant activity in the CNS. Caffeine appears to block adenosine A₁ and A_{2a} receptors, producing a psychomotor stimulant effect. Because of the high levels of A_{2a} receptors in the striatum, the potential use of caffeine for the treatment of Parkinson's disease has been advanced. Since adenosine A_{2a} receptor blockade appears to protect dopaminergic neurons from toxic agents, a neuroprotective role has been proposed for caffeine in the treatment of Parkinson's disease. Caffeine intake has also been associated with a decreased risk of Alzheimer's disease, again presumably acting as a neuroprotective agent [12].

2.6.5 Nicotine

It is an alkaloid found in abundance in tobacco and eggplants. It is metabolized in the liver and its main metabolite is cotinine. With smoking low doses of nicotine exerts its effects on sympathetic (tachycardia, high blood pressure) and parasympathetic (tonus in the digestive system, increases in peristaltic movements and acid secretion) effects. (Thromboxane A₂ increase, lipolysis, psychomotor stimulation, decreases appetite, analgesic effect, increases the secretion of ADH, ACTH, cortisol and insulin, decreases secretion of LH and PRL). Causes psychological and physical addiction. Inhaled nicotine in cigarette smoke is known to permeate the lungs

where more than 80% of the available nicotine is absorbed into the bloodstream. After absorption into the blood, nicotine readily crosses the blood– brain barrier and appears to be rapidly partitioned into brain tissue. Concentrations of nicotine in the brain have been reported to be 5–7 times higher than blood concentrations. Smokers assert that, in addition to its positive effects on concentration and attention, the primary positive effect of smoking is that it calms and relaxes. Recent findings suggest that one of the sites of action of nicotine may be in the RAS, specifically, on PPN neurons. Nicotine, at least initially, has an inhibitory effect on cholinergic RAS neurons, which could produce the calming effect reported upon inhalation of cigarette smoke. The majority of cigarettes are consumed by the mentally ill, especially those with disorders involving hypervigilance or hyperarousal, such as schizophrenia, anxiety disorders, and depression. That is, smoking may be a form of self-medication, presumably because of its calming effects. This effect (inhibition of cholinergic RAS neurons) appears to differ from the role of smoking in reducing the incidence of Parkinson's disease, which appears to be manifested as a neuroprotective action on dopaminergic neurons by nicotine. Cerebral vasodilation is seen immediately after smoking, but chronic smokers show global reductions in cerebral blood flow. Considering that hypofrontality is present in schizophrenia, anxiety disorders, and depression, the initial beneficial, calming effects of nicotine may be followed by deleterious consequences on cortical blood flow. Such an effect may drive craving for the next cigarette, creating a vicious cycle of continuous self-administration [12, 58, 59].

2.6.6 Stimulants

The most commonly used stimulant, amphetamine, induces release of monoamines, especially dopamine, but also blocks their reuptake and may have neurotoxic effects on nigral neurons and, more recently, is suspected of inducing the degenerations of certain striatal neurons. Unfortunately, this agent is abused for recreational purposes and continues to be prescribed for the treatment of attention deficit disorder (ADD). Fortunately, methylphenidate does not appear to have such neurotoxic effects, although its use has decreased.

Non-amphetamine stimulants: Modafinil- has been specifically produced for the treatment of narcolepsy. Modafinil is a newer stimulant that does not appear to act through dopaminergic mechanisms, like amphetamine. Modafinil does seem to affect structures involved in the regulation of sleep– wake states and to affect a number of transmitter systems, including noradrenergic, histaminergic, and orexinergic, as well as excitatory amino acid and serotonin release. In addition, it may block GABA_A receptors [60–62].

2.6.7 Schizophrenia, anxiety disorder and depression

Hypofrontality, hypervigilance and sleep irregularities are common symptoms for these disorders. Regions in relation with RAS (cholinergic PPN, noradrenergic LC and serotonergic RN) that we tried to tackle so far, their neurotransmitters and pharmacological agents that are effective on their receptors are used for the treatment of these symptoms. The serotonergic RN is known to inhibit the PPN and LC, with the cholinergic PPN exciting the LC and the noradrenergic LC inhibiting, via alpha-2 adrenergic receptors, the PPN. The PPN sends excitatory cholinergic projections to the substantia nigra (SN), which, in turn, sends dopaminergic projections to the striatum. The treatment of depression previously included tricyclic antidepressants such as amitriptyline, imipramine, and clomipramine, agents that mainly blocked reuptake of noradrenaline and serotonin, and blocked histamine

and acetylcholine release, thus accounting for increased sleepiness. The selective serotonin reuptake inhibitors (SSRIs) more selectively affect the RAS by increasing the inhibition. It is not clear if the etiology of depression is related to disinhibition of the PPN and LC by a decrement in serotonergic tone, although this would seem a likely origin for the sleep–wake symptomatology of depression. The treatment of anxiety disorder is involved the use of benzodiazepine amplification of GABAergic inhibition. In addition, the use of the alpha-2 noradrenergic receptor agonist clonidine produces anxiolytic effects, probably by inhibiting autoreceptors in the LC and postsynaptic receptors in the PPN, thus downregulating vigilance. Because of the peripheral cardiovascular effects of clonidine, alpha-2 adrenergic receptor agonists without such actions would be more desirable. One study provided strong evidence for the use of the alpha-2 adrenergic receptor agonist dexmedetomidine as an anxiolytic for the treatment of anxiety disorders like posttraumatic stress disorder, panic attacks, and general anxiety disorder [32]. The etiology of anxiety disorder has been proposed to include downregulation or degeneration of LC outputs (possibly induced by stress hormones), which would act to release, or disinhibit, PPN neurons at site.

The etiology of schizophrenia has been suggested to include increased PPN output, accounting for marked hypervigilance and hallucinations. Excessive PPN output would overactivate the SN and, in turn, increase striatal release of dopamine that is, complying with the dopamine theory of schizophrenia. SWS are reduced in schizophrenics. Consistent with this assumption, lower SWA has been more often reported in institutionalized patients with profound cognitive impairment as well as in schizophrenia patients with prominent negative symptoms. The treatment of schizophrenia previously involved the use of the dopaminergic receptor blocker haloperidol, which induced tardive dyskinesia, among other serious side effects. Newer antipsychotics such as risperidone and quetiapine appear to block dopaminergic, noradrenergic, and serotonergic receptors. More striking antipsychotic effects were provided by the use of clozapine, which was designed as a muscarinic cholinergic blocker for the treatment of Parkinson's disease [14, 63–65].

2.6.8 Motor and non-motor degenerative diseases (amyotrophic lateral sclerosis, Parkinson's disease)

ALS is an incurable neurodegenerative disorder of upper and lower motor neurons, which is characterized by degeneration of the corticospinal tracts, resulting in loss of motor neurons in the brain, brainstem and anterior horn cells of the spinal cord. Loss of motor neurons in the brainstem and spinal cord causes weakness of the pharyngeal, laryngeal, intercostal and diaphragmatic muscles. During non-REM sleep, muscle tone is decreased and during REM sleep muscle tone is almost completely lost. Automatic ventilation during sleep is almost completely dependent on the diaphragm (particularly in REM sleep) therefore diaphragmatic dysfunction (such as that seen in ALS) can predispose to hypoventilation and nocturnal hypoxemia. Parkinson Disease [PD] is the second most common neurodegenerative disorder after Alzheimer's disease. PD occurs as a result of chronic, progressive decrease in dopamine levels of the substantia nigra, secondary to loss of dopaminergic neurons in the pars compacta and the occurrence of Lewy bodies in the cytoplasm of remaining neurons. It is primarily diagnosed clinically and patients may present with the characteristic motor deficits, which include the resting tremor, bradykinesia, rigidity and postural instability. However, most will have both motor and nonmotor symptoms. The nonmotor symptoms cause disturbances, which affect sleep, mood, cognition, sensation and autonomic function. Among the nonmotor symptoms in PD, sleep disorders are second in frequency only to neuropsychiatric disorder [16, 65–68].

2.6.9 Analytical functions of molecules affecting sleep in neurophysiology and physiopathology

Particular attention to hormonal conditions is warranted. After all, the first sign of puberty is pulsatile hormone (LH) release during sleep. For example, narcolepsy is tightly linked with certain human leukocyte antigen (HLA) haplotypes, suggesting that it is an autoimmune disorder. Kleine–Levin syndrome, discussed earlier, is linked to similar haplotypes, which suggests an autoimmune etiology. Interestingly, in most cases of narcolepsy, Kleine–Levin syndrome, as well as schizophrenia, panic attacks, obsessive–compulsive disorder, and other disorders, the age of onset is soon after puberty. Along other lines, in about 20% of schizophrenic patients, the mother had an influenza attack during the second trimester, while narcoleptics are born predominantly during the late winter–early spring, that is, after influenza season. It has been suggested that developmental dysregulation, either pre- or perinatally (initial insult), becomes pathologically manifest after exposure to puberty and its hormonal onslaught. These considerations point to complex interactions between development, environment, and hormonal status, all of which seem to affect sleep–wake regulation in as yet unknown ways. These findings suggest that the effects of hormones, either prescribed or taken as dietary supplements, or abused, need to be more closely studied and considered in the design of therapeutic interventions [69, 70].

Brain energy requirements are extraordinarily high; any modification in glucose utilization by the brain may profoundly affect glucose tolerance. Cerebral glucose utilization is lower during SWS than during either REM sleep or wake. Using PET scans, a strong correlation was evidenced between slow-wave activity, an index of the intensity of SWS, and regional blood flow in the prefrontal brain. Furthermore, experimental studies, involving continuous enteral nutrition or intravenous glucose infusion while allowing for normal nocturnal sleep, have shown that glucose tolerance is minimal during the first half of the sleep period, i.e. when SWS is the dominant sleep stage. These findings confirm the existence of a robust link between SWS and glucose tolerance. Both reduction in total sleep duration with slow-wave sleep (SWS) largely preserved and alterations of sleep quality (especially marked reduction of SWS) with preservation of total sleep duration are associated with insulin resistance without compensatory increase in insulin secretion, resulting in impaired glucose tolerance and increased risk of type 2 diabetes. When performed under rigorously controlled conditions of energy intake and physical activity, sleep restriction is also associated with a decrease in circulating levels of leptin (an anorexigenic hormone) and an increase in circulating levels of ghrelin (an orexigenic hormone), hunger and appetite. Furthermore, sleep restriction is also associated with a stimulation of brain regions sensitive to food stimuli, indicating that sleep loss may lead to obesity through the selection of high-calorie food. There is also evidence that sleep restriction could provide a permissive environment for the activation of genes that promote obesity. Indeed, the heritability of body mass index is increased in short sleepers. Thus, chronic sleep curtailment, which is on the rise in modern society, including in children, is likely to contribute to the current epidemics of type 2 diabetes and obesity [71–73].

Chronic sleep loss is increasingly common in industrialized societies, affecting about 45% of adults. Sleep deprivation induces behavioral, hormonal, and neurochemical alterations. The stress inherent in sleep deprivation causes changes in the concentration of hormones such as cortisol as well as in prolactin and estradiol, which are known to influence dopaminergic transmission.

Studies have suggested that dopamine (DA) is responsible for the behavioral changes observed after sleep deprivation. Specifically, REM sleep deprivation has

been shown to be related to changes in D2 post-synaptic receptor sensitivity in the rat striatum. DA transporter (DAT) knockout mice exhibit increased wakefulness and less SWS. REM sleep would induce increases in dopaminergic activity after sleep deprivation and selective REM sleep deprivation for a prolonged period would result in down-regulation of DAT, enhancing dopaminergic neurotransmission. Amphetamine derivatives inhibit DAT-mediated DA reuptake [74, 75].

Short-term sleep deprivation has shown therapeutic properties for with mood disorders, long-term/ chronic sleep deprivation and disruption have instead been related to the development of mood disorders via monoamine (5-HT, NE, DA) activity dysregulation. The main symptoms of depression are due to a functional deficiency of the brain monoaminergic transmitters: norepinephrine, serotonin and/or dopamine, whereas mania is caused by a functional excess of monoamines at critical synapses in the brain. Although recently some observations have challenged the legitimacy of this theory, a dysregulation in monoamine production and transmission is still considered an important factor in the regulation of mood, emotions, cognition, motivational behaviors and stress responses. Deuschle et al. [81] conducted a study in a group of individuals suffering from chronic insomnia, and found that the short allele of the 5-HT transporter was significantly more frequent in patients suffering from insomnia than in good sleepers. Roman et al. [82] suggested that chronic sleep restriction may increase an individual's vulnerability to develop mood disorders by impairing serotonergic transmission throughout the activation of the stress system. The genetic makeup of the dopamine system involved in vulnerability to mood disorders has also been shown to be involved in the response to sleep loss and in alterations in responses to reward in humans. A polymorphism in the dopamine 2 receptor, more commonly in the dopamine transporter system, has been related to a vulnerability to psychiatric disorders in the presence of sleep deprivation in humans. It has been widely shown that individuals suffering from insomnia display hyperactivation of the hypothalamic–pituitary–adrenal-axis at both brain and peripheral levels. Increases in norepinephrine, epinephrine and other markers of sympathetic outflow have been related to cognitive and emotional arousal and somatic hyperarousal in individuals suffering from insomnia: it is the key pathophysiological mechanism of insomnia. Changes observed in brain structures in individuals suffering from insomnia include a reduction in the volume of the prefrontal cortex, caudate head and hippocampus, as well as an increase in the amygdala volume, modifications resembling those described in individuals suffering mood disorders. Given these similarities, it has been hypothesized that insomnia may influence the development and maintenance of a mood disorder throughout the activation of the stress system and of its negative consequences on the brain, including hippocampal neurogenesis, synaptic plasticity and connectivity [76–85].

Finally, we can talk about the relationship between sleep and antidepressants, which are effective on monoamine (5-HT, NE, DA) activity systems in the brain: (1) Tricyclic antidepressants (TCA) (antagonist of 5HT-1, NE, M1, H1 receptors); (a) tertiary TCAs shorten sleep latency and reduce awakenings during sleep. Therefore, it is perceived as a sedative; doxepin and amitriptyline decrease REM rate in sleep EEG, cause prolongation of REM sleep latency, (b) Secondary TCAs such as desipramine are less sedative and relatively stimulating, (c) potent serotonergic TCAs such as clomipramine increase eye movements in NREM. It increases the periodic leg movements during sleep, (2) nonspecific reuptake inhibitors (5HT, NE DA); trazadone is sedative and nefazodone is less sedative, they increase SWS sleep, (3) monoamine oxidase inhibitors (MAOI) (eg, tranylcypromine, moclobemide), (4) selective serotonin reuptake inhibitors SSRI (eg, fluoxetine, escitalopram, paroxetine, sertraline), (5) serotonin and norepinephrine reuptake inhibitors (SNRI) (eg, venlafaxine, duloxetine, reboxetine)

(6) Bupropion (inhibition of norepinephrine and dopamine reuptake) these agents increase SWS, prolong REM latency, shorten REM time, (7) Agomelatine (agonism at melatonin M1 and M2 receptors, antagonism at serotonergic 5-HT_{2C} receptors) have been found to increase SWS [86–89].

2.6.10 Conclusion

The more we learn about the neurophysiology of sleep and the effects of related molecules, the better we understand the pathological processes in wakefulness. Understanding the functioning of the sleep brain, along with neurotransmitters, hormones, and new molecules, will explain unknown physiological processes and inspire innovative processes in pharmacology.

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