Chapter 4
The Role of Sleep in Homeostatic Regulation of Ionic Balances and Its Implication in Cognitive Functions

Fayaz Ahmad Mir, Sushil K. Jha, and Vibha M. Jha

Abstract Several studies have suggested that physiological sleep is an indispensable part of the system. It is, however, not known what sleep does to our brain and body. Sleep helps to modulate transcription and translational processes, synaptic neurotransmission, metabolic processes, detoxification, restitution, proliferation, thermoregulation and neuro-immuno-endocrine information, stress reactions, emotional fluctuations, growth, timekeeping, and strategy for survival. In addition, evidences suggest that sleep could be involved in the maintenance of inter- and intracellular microenvironments. Sleep may modulate the homeostatic regulation of (a) acid-base balance, (b) biological buffer system, and (c) ionic/electrolytic balances. We have proposed earlier that one of the essential functions of REM sleep could be to maintain normal bodily CO_2 level during sleep. The elevated bodily CO_2 level during prolonged vigilant states can adversely alter the cellular ionic milieu. Therefore, it is essential that the level of CO_2 must remain within physiological limits, and sleep seems to play an essential role in the maintenance of physiological CO_2 level. Furthermore, sleep may also be playing an essential role in maintaining homeostatic balance of several ions such as iron, calcium, potassium, sodium, zinc, magnesium, etc. In this chapter, we discuss the role of sleep in the maintenance of ionic and acid-base balances. We have also addressed how the chronic and acute sleep loss can cause ionic imbalances leading to cellular distress. Further, we have attempted to highlight the influence of ionic homeostatic dysregulation on cognitive performances.

Keywords Acid-base balance · Energy homeostasis · Learning and memory · Respiratory acidosis · NREM sleep · REM sleep and sleep deprivation

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4.1 Introduction

How sleep should be defined is still debatable. Nonetheless, it is considered to be a reversible behavioral state, during which, the perception of the sensory stimuli, consciousness, and activity of voluntary muscles remains subdued (Carskadon and Dement 2005). Electrophysiologically, it has been characterized broadly into two stages: non-rapid eye movement (NREM) and rapid eye movement (REM) sleep (Aserinsky and Kleitman 1953). Two distinct sleep states have been characterized only in terrestrial mammals and birds (Madan and Jha 2012b), and it is unclear why these distinct sleep states have evolved only in phylogenetically advanced animals. Although several studies have suggested that physiologically, sleep is an indispensable part of the system, what sleep does to our brain and body is still under study.

Several theories have been put forward regarding the functions of sleep. It has been proposed that sleep helps to modulate transcription and translational processes at the molecular level; synaptic neurotransmission at the subcellular level; metabolic processes, detoxification, restitution, and proliferation at the cellular level; thermoregulation and neuro-immuno-endocrine information processing at the physiological level; stress reactions and emotional fluctuations at the psychological level; immune and host defense responses at the pathological level; pregnancy and lactation at the reproductive level; growth and timekeeping at the whole body level; and strategy for survival at the evolutionary level (Inoue et al. 1995; Cirelli 2002, 2013; Guzman-Marin et al. 2003; Madan and Jha 2012a, b, 2014; Vecsey et al. 2012). The available knowledge thus allows us to believe that sleep has multidimensional functions.

Some current evidence suggests that sleep could be involved in the maintenance of inter- and intracellular microenvironments. Sleep may modulate the homeostatic regulation of (a) acid-base balance, (b) biological buffer system, and (c) ionic/electrolytic balances. We have proposed earlier that one of the essential functions of REM sleep could be to maintain normal bodily CO_2 level during sleep (Madan and Jha 2012a). In addition, it has been found that moderate increase in ambient CO_2 level induces NREM sleep (Fraigne et al. 2008). The elevated bodily CO_2 level during prolonged vigilant states can adversely alter the cellular ionic milieu. Therefore, it is essential that the level of CO_2 must remain within physiological limits, and sleep may be playing an essential role in the maintenance of physiological CO_2 level (Madan and Jha 2012a). In this chapter, we discuss the role of sleep in the maintenance of homeostatic ionic and acid-base balances. We have also addressed how the chronic and acute sleep loss can cause ionic imbalance and cellular distress. Further, we have attempted to highlight the influence of ionic homeostatic dysregulation on cognitive performances.

4.2 Acid-Base Balance

Before we discuss the role of sleep in homeostatic regulation of acid-base balance, it would be imperative to know about the ionic regulatory machinery. One of the most essential homeostatic mechanisms is the one regulating the concentration of hydrogen ions (pH) in the body fluids. Biological pH is tightly regulated by various mechanisms, such as the changes in the respiratory rate, the buffering capacity of the protein molecules present in the body fluid, and the buffer systems (phosphate and bicarbonate buffers) that exist in our body. The various types of machinery are essential because every cellular reaction occurs at an optimal pH. The structure and functions of proteins present in the intracellular and extracellular compartments are susceptible to pH alterations. Changes in body pH may lead to pathophysiological conditions such as stroke, seizures, pain, anxiety, meningitis, tumors, trauma, severe anemia, hepatic and cardiac failure, etc. (Das 2003). Therefore, the pH of extracellular fluids must be tightly controlled within narrow ranges for optimal cellular function.

The alterations in bodily pH occur mainly because of two etiological factors: respiratory acidosis/alkalosis and metabolic acidosis/alkalosis. Hydrogen/hydroxyl ions reversibly bind to various extracellular and intracellular buffering agents, for example, proteins (hemoglobin), bicarbonate buffer, phosphate buffer, etc. and resist pH change (Stewart 1978). The pH of the blood mainly decreases because of either (a) high levels of CO_2 production through metabolism or (b) hypoventilation. Increase in carbon dioxide (CO_2) levels in the body raises the hydrogen ion (H^+) concentration and decreases the pH of blood. The increased CO_2 level in the body stimulates central respiratory centers, which increase the breathing rate at the first place to remove excess CO_2. The increased breathing rate expels more CO_2 from the body, which ultimately depletes H^+, and finally, the blood pH gets back to normal. This is how our sensitive respiratory system is involved in the regulation of H^+ concentration (Das 2003).

4.2.1 Sleep and Respiratory Acidosis

Sleep plays an essential role in preventing respiratory acidosis. Respiratory acidosis is usually caused by the alveolar hypoventilation, which increases arterial partial pressure of carbon dioxide, thereby decreasing blood pH (Böing and Randerath 2015). Although blood pH is maintained within tight physiological limits, it varies across day and night and exhibits diurnal alterations. It has been reported that the pH of blood increases after meal and decreases during sleep (Rune and Lassen 1968). In addition, it has been found that ventilation rate and blood pH remain at a lower level during NREM sleep (McKay et al. 2010; Madan and Jha 2012a). Hypercapnia (high CO_2 level) has been observed during sleep prior to wakefulness, and also the minute ventilation rate decreases from wakefulness to NREM sleep (Böing and Randerath

2015). Besides the bodily changes in CO_2 level across sleep-wake states, the ambient change in CO_2 level also influences sleep pattern. For example, mild increase in CO_2 level (2%) in the surroundings induces total sleep with a concomitant increase in REM sleep frequency, while high level of CO_2 (6–8%) in the ambience significantly decreases total sleep amount (Fraigne et al. 2008). Rhythmic changes in CO_2 and blood pH level across sleep-wakefulness and the influence of ambient CO_2 level on sleep suggest that there would be a close link between the chemosensory and sleep machineries and can affect each other through some common pathways.

The central chemosensory system is located in the brainstem medullary area (Squire et al. 2013). Neurons in the brainstem nuclei such as the locus coeruleus (LC), retrotrapezoid nucleus (RTN), solitary tract nucleus (NTS), and dorsal raphe nucleus (DRN) sense the changes in hydrogen ion concentration in the extracellular fluids and accordingly stimulate the breathing centers. This in turn alters the breathing rates to bring the altered level of CO_2 in a normal range (Bruce and Cherniack 1987; Arita et al. 1989; Nattie and Li 2009; Squire et al. 2013). The central chemosensory system modulates breathing rate (hyper- or hypoventilation) depending upon the changes in the pH of extra- or intracellular fluid through the inspiratory and expiratory neurons and also rhythm generating brainstem neurons (Taylor et al. 1999; Nattie and Li 2009; Smith et al. 2015). Interestingly, the chemosensory circuitries, which involve the LC, DRN, etc., are also a part of the ascending reticular arousal system (Jha and Mallick 2011; Madan and Jha 2012a). The DRN and LC areas contain wake-active neurons, which are maximally active during wakefulness, and their firing rate slows down during transition from wake to NREM sleep. They remain moderately active during NREM sleep but cease firing during REM sleep (for review see (Jha and Mallick 2011; Madan and Jha 2012a). The expression patterns of NREM and REM sleep significantly alter with the LC and DRN ablation (McGinty and Harper 1976; Schwartz et al. 2016). In addition, DRN and LC lesion in adult animals or early during the prenatal period reduces CO_2-mediated induction of physiological responses (Nattie and Li 2009). These studies further suggest that the two primary brainstem nuclei, the LC and DRN, play an essential role in the regulation of sleep as well as chemoreception.

Furthermore, the brainstem damage because of acute infarction, stroke, etc. causes sleep-disordered breathing (SDB) (Brown et al. 2014). One of the examples of SDB is obstructive sleep apnea (OSA), which is primarily characterized by repetitive episodes of complete or partial obstruction of airflow during sleep. Interestingly, it has been found that serotonin and norepinephrine levels are altered in OSA patients (Ozaki et al. 1986; Cui et al. 2012). The diaphragm and genioglossus respiratory muscles help in normal breathing, and the phrenic nerve through the cervical C3, C4, and C5 areas innervates these diaphragm muscles. The nerve conduction velocity of the phrenic nerve is considered a good indicator of diaphragm function (Cui et al. 2012). An altered activity of the diaphragm and genioglossus muscles has been found in OSA patients (Cui et al. 2012). Although it is not known how the activity of these muscles alters, it is believed that the altered level of serotonin and norepinephrine in OSA patients could be associated with breathing disorder (Ozaki et al. 1986; Mahamed and Mitchell 2007; Cui et al. 2012). Thus, it

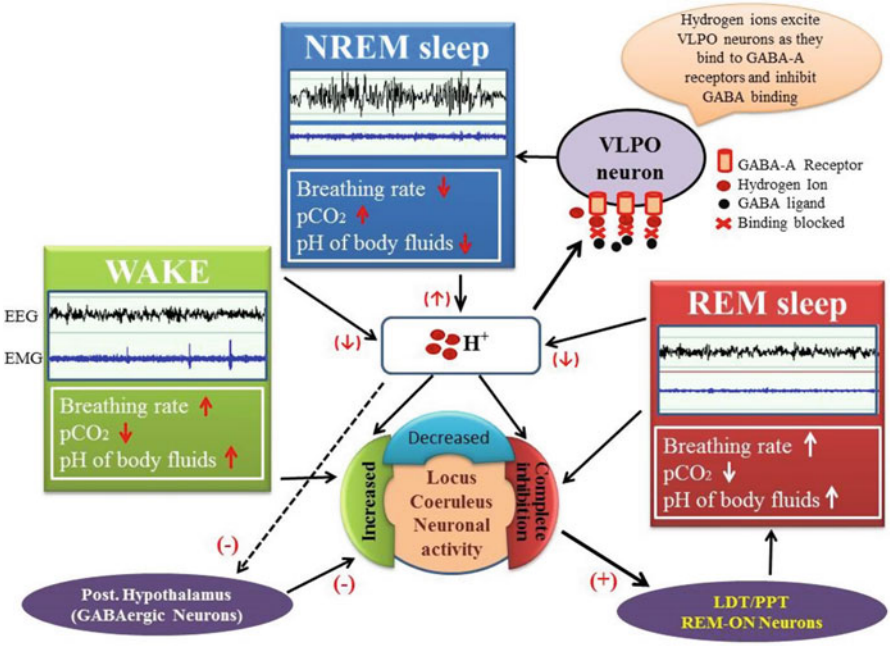

Fig. 4.1 The proposed model explains the changes in the hydrogen ion level across sleep-wake cycle and influence of increased hydrogen ion concentration on NREM sleep and REM sleep generation. *Abbreviations*: *LDT* laterodorsal tegmentum, *PPT* pedunculopontine tegmentum

seems that the DRN and LC not only modulate sleep and chemoreception but are also associated with the pathophysiology of sleep-related breathing disorders.

The brainstem nuclei, such as the LC, have a high proportion (>80%) of wake and chemosensitive neurons (Aston-Jones and Bloom 1981; Pineda and Aghajanian 1997). These neurons are highly active during wake and normocapnia, but the firing rate significantly alters with the change in behavioral state or CO_2 level (Madan and Jha 2012a). For example, mild hypercapnia excites the LC neurons, while acute hypercapnia hyperpolarizes LC neurons (Dean et al. 2001). It is not known if the wake- or REM sleep-related neurons in the LC are also chemosensitive in nature, but it appears that some of the neurons may be participating in both the functions. The REM-OFF neurons cease their activity during REM sleep, but it is not known how REM-OFF neurons become hyperpolarized during REM sleep. One of the possible reasons that can be attributed to the alteration in the firing rate could be the changes in the H^+ ion concentration in and around the LC neurons during sleep. It has been observed that the minute ventilation rate reduces and upper airway resistance increases at NREM sleep onset, which can increase H^+ ion concentration in the brain (Fig. 4.1) (McKay et al. 2010). An elevated H^+ ion concentration if sustained for a while during the stable and lengthy episodes of NREM sleep, it may switch off LC's REM-OFF neurons for REM sleep genesis. Therefore, it is likely that the elevated CO_2 level within a set range during stable NREM sleep episodes may

hyperpolarize REM-OFF neurons. We have proposed that one of the functions of REM sleep could be to help prevent the induction of hypercapnia during sleep (Madan and Jha 2012a).

These studies suggest that chemoregulatory and sleep machinery are closely linked. An alteration in either system may influence the other. For example, sleep fragmentation alters blood pressure and heart rate variability (Carrington and Trinder 2008). Sleep deprivation may induce acid-base homeostatic imbalance (Madan and Jha 2012a). On the other hand, different ions may also influence sleep architecture (Held et al. 2002). There is a definite evidence suggesting that the two independent systems are closely linked. We will now highlight the possible role of sleep in the maintenance of ionic balances. We will also point out how sleep deprivation alters the cellular environment. Further, we will attempt to discuss the possible impact of alteration in cellular milieu on cognitive ability.

4.3 The Role of Sleep in Hemoglobin's H^+ Buffering Capacity

Almost all proteins can function as buffers. The positively charged amino groups and negatively charged carboxyl groups of amino acids of proteins can bind hydrogen and hydroxyl ions and thus function as buffers. In erythrocytes, carbonic anhydrase enzyme converts CO_2 and H_2O into carbonic acid (H_2CO_3), which is finally dissociated into H^+ and HCO_3^-. The liberated hydrogen ions are then buffered by hemoglobin. In the pulmonary capillaries, the conversion process is reversed, and CO_2 is formed from the H^+ and HCO_3^-, which is exhaled into the atmosphere. The buffering capacity of hemoglobin thus plays a vital role in the maintenance of blood pH within physiological limits.

Some studies suggest that altered sleep-wake pattern can affect the structural and functional properties of hemoglobin. It has been found that acute sleep loss (24 h) is associated with high level of glycated hemoglobin (HbA1c) (Kachi et al. 2011). Under the persisted hyperglycemic condition, hemoglobin binds to glucose molecules. Once glucose molecule binds to hemoglobin, it does not dissociate, and the hemoglobin remains glycated (Ye et al. 2016). Surprisingly, the high level of HbA1c is significantly correlated with chronic early morning awakening and poor sleep quality (Kachi et al. 2011). Kachi et al. (2011) have reported a high level of HbA1c in the blood of clinically insomniac as well as patients having milder forms of insomnia. Insomniac patients having a high level of HbA1c were not suffering from any other diseases such as diabetes, hypertension, etc. However, they have not observed any significant association between the level of HbA1c and altered sleep latency (Kachi et al. 2011). Hence, it was argued that high level of HbA1c might not have influenced sleep properties; instead, poor sleep quality would have altered the properties of hemoglobin.

Sleep deprivation can alter the properties of hemoglobin, but whether it affects the buffering capacity of hemoglobin is an intriguing question. It has been found that

24 h sleep deprivation affects the ventilatory response and bodily CO_2 level (Schiffman et al. 1983). Schiffman et al. (1983) have argued that a decline in hypercapnia-induced ventilatory response could be attributed to a decrease in ventilatory drive but not to the changes in lung mechanics (Schiffman et al. 1983). On the other hand, the high proportion of HbA1c has been observed in patients suffering from diabetes and kidney diseases (Shadman et al. 2013; Kang et al. 2015). Surprisingly, these patients were also diagnosed with altered ventilatory response to hypercapnia and ventilatory drive (Williams et al. 1984). Furthermore, structural and functional alteration has been observed in sugar-bound hemoglobin HbA1c (De Rosa et al. 1998). It has been observed that (a) the low-affinity conformation (or T-state) of HbA1c is destabilized by the chemical modification and (b) the "Bohr effect" is reduced with respect to that of native hemoglobin (HbA0) (De Rosa et al. 1998). The reduced Bohr effect in hemoglobin changes the acidic or alkaline nature of hemoglobin, which may affect its buffering capacity (Thom et al. 2013). Since the Bohr effect is reduced in the HbA1c, it can be assumed that it may have reduced the buffering capacity. Since early morning awakening or poor sleep quality causes glycosylation of hemoglobin, which may have an inadequate buffering capacity, it is possible that sleep modulates the ionic buffering properties of hemoglobin.

In addition, studies suggest that hematocrit value (percent RBC in the blood) is significantly high in severe OSA patients (Choi et al. 2006). Treating sleep apnea patients with continuous overnight positive airway pressure (CPAP) reduces the hematocrit value (Krieger et al. 1990). Abnormally poor sleep quality is manifested in sleep apnea patients (Macey et al. 2010), and CPAP treatment also improves sleep amount in these patients. These results further suggest that poor sleep quality may influence the blood dynamics and hemoglobin properties.

4.3.1 Sleep Deprivation and Changes in Protein Buffering Capacity

Based on the pH of extra-/intracellular fluid, the carboxyl and/or amine group side chains of amino acids in proteins can act as a proton donor or proton acceptor. At a normal body pH, most carboxyl groups exist as COO^- and can accept hydrogen ions, if the pH begins to drop. Similarly, histidine and cysteine amino acids have COOH at normal body pH and can donate hydrogen ion, if the pH begins to rise. This is how most proteins buffer acid or base and help regulate pH of the extracellular and/or intracellular compartments.

Changes in the level of specific proteins in the organelles under a particular situation, such as sleep deprivation, may influence the acid-base balance. Changes in proteome levels in the entire brain have been examined by using advanced quantitative proteomic technologies. It has been found that the level of nearly 10,000 proteins is altered after sleep deprivation. Surprisingly, the majority upregulated proteins were associated with mitochondria and energy metabolism (Ren et al. 2016). Furthermore, the mitochondrial uncoupling proteins UCP2 and

UCP3 also increased after sleep deprivation in the liver and skeletal muscle (Cirelli and Tononi 2004). The uncoupling proteins UCP2 and UCP3 are mitochondrial anion-carrier proteins, which play an essential regulatory role in the generation of reactive oxygen species (ROS) from the electron transport chain. The overproduction of ROS by the respiratory chain activates UCP2 and UCP3 proteins, which in turn augments proton leak from the mitochondrial membrane (Mailloux and Harper 2011). The alteration in the proton-motive force across the mitochondrial membrane influences proton gradient and ultimately mitochondrial pH (Dzbek and Korzeniewski 2008). Since the level of UCP2 and UCP3 proteins increases after sleep deprivation, which enhances proton leak across the mitochondrial membrane, suggesting that sleep deprivation may affect the proton-motive force and mitochondrial pH. Furthermore, the increased level of ROS production is also associated with an alteration in mitochondrial pH regulation and sleep deprivation (Ramanathan et al. 2002; Milner et al. 2007). It has been found that sleep deprivation significantly decreases the activity of superoxide dismutase (SOD) enzyme, and decreased SOD activity causes increased production of ROS (Ramanathan et al. 2002). On the other hand, it has been reported that the changes in ROS level influence the activity of Na^+/H^+ exchanger and thereby alter intracellular acidification (Milner et al. 2007). These results indicate that sleep deprivation causes an acid-base homeostatic imbalance at least at the organelle level, which could be attributed to sleep-deprivation-mediated changes at the proteome level.

4.4 Sleep and Electrolytic Ionic Balance

Sleep may also have a role in the maintenance of bodily electrolytic balance. Electrolytic ions such as sodium, potassium, chloride, bicarbonate, phosphate, magnesium, calcium, etc. are vital for cellular functioning and are required for various biochemical and enzymatic reactions. These ions are also necessarily required for efficient performance of several physiological processes, for example, neurotransmission, muscle contraction, heart function, etc. The excitable cells, such as neurons and muscle cells, require the movement of Na^+ and K^+ ions across the membrane to maintain and generate the membrane action potential. Interestingly, it has been observed that sleep deprivation causes electrolytic imbalances within the body, which ultimately lead to many pathophysiological conditions. Many reports suggest that sleep plays a vital role in the homeostatic regulation of ionic balances either directly or through modulation of neuroendocrine functions (Fig. 4.2).

The neuroendocrine system, which regulates bodily ionic balances, involves mineralocorticoid hormones. Aldosterone is one of the mineralocorticoid hormones, which is synthesized and released mainly by the zona glomerulosa cells of the outer layer of the adrenal gland. The adrenal gland releases aldosterone primarily in response to angiotensin II, which in turn induces sodium reabsorption by activating the apical epithelial sodium channel and the basolateral Na^+-K^+-ATPase pump in the

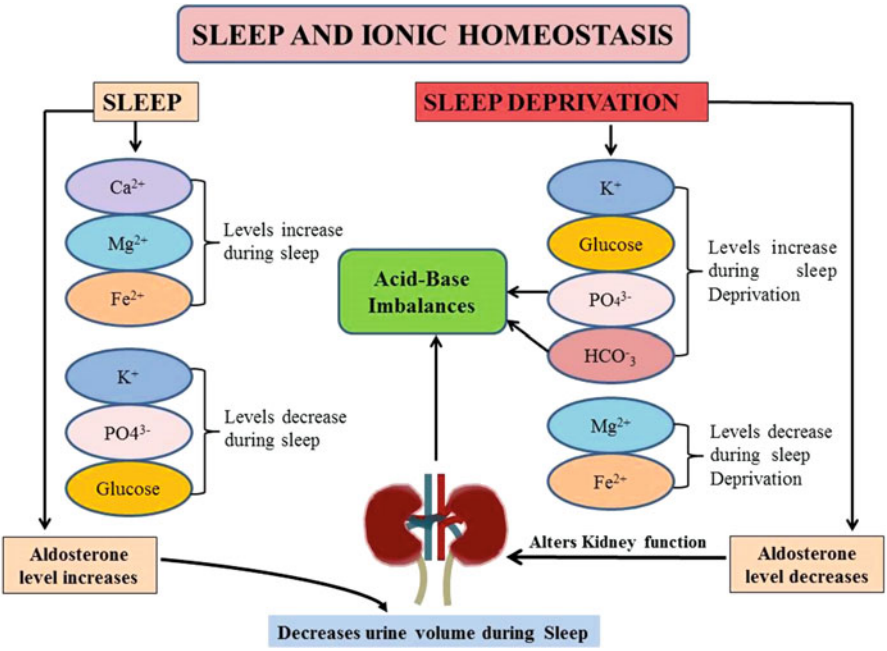

Fig. 4.2 Changes in the level of aldosterone and various other ions during sleep and sleep deprivation. Sleep possibly plays a major role in the maintenance of ionic and acid-base balances

distal nephron (Briet and Schiffrin 2010). Thus, it plays a significant role in the maintenance of sodium balance.

4.4.1 Aldosterone Release Is Augmented during Sleep

Interestingly, it has been observed that aldosterone secretion is modulated by two primary hormonal systems, i.e., the renin-angiotensin system and the adrenocorticotropic system. It has been reported that the peak release of aldosterone shows a synchronous pattern with cortisol peak, which occurred during late sleep and early morning hours (Katz et al. 1972). Furthermore, highest release of aldosterone (both high pulse amplitude and pulse frequency) has been observed during sleep and reduced release of aldosterone during sleep deprivation (Charloux et al. 1999). In addition, it has been found that among the two hormonal systems that influence aldosterone pulsatility, the renin-angiotensin system plays a significant role during sleep in the maintenance of water and salt during the night (Charloux et al. 1999).

4.4.2 Sleep Enhances Sodium Ions and Water Reabsorption

Sodium ions are required for many physiological processes like bodily water/fluid balance, nerve conduction, cardiovascular functions, muscle contraction, etc. The average sodium concentration in a cell is about 15 mmol, which may vary in different organs (Boundless 2016). It is essential that the sodium concentration should be maintained within the physiological limit. Altered sodium levels are involved in several diseases, for example, patients with acute hyponatremia develop neurologic symptoms such as cerebral edema induced by water movement into the brain, seizures, impaired mental status or coma, and death. Similarly, chronic hyponatremic patients exhibit gastrointestinal tract symptoms such as nausea, vomiting, loss of appetite, some neurologic abnormalities, etc. (Sahay and Sahay 2014). Hypernatremia apart from causing hypertension, brain hemorrhage, and dehydration is also associated with hyperglycemia and mild hypocalcemia (Marcdante et al. 2010). Furthermore, hypertension, caused due to excessive sodium intake, is linked to cognitive deficits (Miller et al. 1968; Grodstein 2007). Therefore, it is imperative that sodium ions should necessarily be maintained at an appropriate concentration in the body.

The homeostatic balance of sodium ions and water is primarily regulated by two hormones: aldosterone and antidiuretic hormone (ADH, also known as vasopressin). As mentioned above, aldosterone increases sodium reabsorption explicitly in the distal convoluted tubule and collecting duct of the nephrons in the kidneys. However, ADH prevents fluid loss and promotes water conservation in the body. The primary stimulus for ADH release from the posterior pituitary gland is an increase in blood osmolarity, which is detected by the osmoreceptors present in the hypothalamus. ADH also stimulates thirst to increase water intake, which lowers blood osmolarity and thus maintaining the electrolytic balance.

Interestingly, it has been observed that the peak amplitude and frequency of release of both aldosterone and ADH occur during sleep. Charloux et al. (1999) have noted that during the regular nighttime sleep periods, the mean aldosterone levels were significantly high during the 11:00 PM to 07:00 AM compared to the 03:00 to 11:00 PM time periods. In the daytime sleep condition, aldosterone levels were higher during the 07:00 AM–03:00 PM compared to wakefulness during the same time periods suggesting that the aldosterone peak is influenced by sleep only rather than circadian timing (Charloux et al. 1999). The release of ADH hormone also increases during the late phase of sleep period (Forsling 2000; Trudel and Bourque 2010). It has been shown that the SCN clock neurons exhibit low neuronal activity during the late phase of sleep. Further, it was found that clock neurons mediate an activity-dependent presynaptic silencing of osmosensory afferent synapses onto ADH neurons. The low firing activity of the SCN's neurons during the late phase of sleep helps obtain the osmoregulatory gain onto ADH neurons. The SCN clock neurons, thus, reversibly modulate the number of functional osmoregulatory synapses and enhance ADH release during the late stage of sleep (Trudel and Bourque 2010).

These studies possibly answer an intriguing question, why we do not feel thirsty while sleeping even for long hours. The underlying reasons could be (a) the high release of aldosterone and (b) ADH hormones during sleep. These two hormones together contribute in water retention in the body. The increased aldosterone level increases renal reabsorption of sodium ions, which in turn elevates osmolality of extracellular fluid. The hypothalamic osmoreceptors sense the changes in osmolality and induce the release of ADH hormone. As a result, water reabsorption from the collecting duct of the kidney is enhanced. The implications of these findings are not limited to obtain the answer of a simple question of not being thirsty during long hours of sleep; it also provides greater insight into how sleep might be involved in rejuvenating almost all the physiological processes.

4.4.3 Sleep Deprivation Alters the Levels of Phosphate Ions in the Body

Phosphate is an intracellular anion predominantly found in several organic moieties and remains bound to lipids, sugars, and proteins molecules. It is involved in several physiological and enzymatic processes in our body. For example, phosphate deficiency leads to tissue hypoxia and cellular dysfunction (Miller and Slovis 2000; Subramanian and Khardori 2000). Alterations in phosphate levels have been implicated in several pathophysiological conditions, such as myalgias, weakness, anorexia, tetany, seizures, coma, rhabdomyolysis, respiratory failure, ventricular tachycardia, etc. (Shiber and Mattu 2002). Besides having several roles in the maintenance of physiological systems, phosphate ions also play an essential role in protein synthesis and its modification and ATP generation.

Studies suggest that sleep also plays a role in the maintenance of cellular homeostatic balance of phosphate ions. It has been found that prolonged sleep deprivation (70–80 h) not only induces changes in the level of some enzymes but also causes hyperphosphatemia (Ilan et al. 1992). Furthermore, phosphate ions are necessarily required for ATP generation, and it has been reported that the surge of ATP production occurs during the initial hours of natural sleep period in wake-active brain areas. The surge is exclusively associated with sleep but not with the time of day. Interestingly, sleep deprivation for 3 or 6 h also altered the generation of ATP (Dworak et al. 2010). These studies suggest that sleep deprivation not only alters the level of phosphate ion but also affects ATP generation.

Parathyroid hormone (1,25-dihydroxy-vitamin D (1,25-(OH)2-D)) plays a vital role in phosphate homeostatic balance through intestinal absorption from the diet and phosphate release from the bone. Chapotot et al. (1996) have studied the 24-h intact parathyroid hormone profile in healthy and sleep-deprived subjects. They found that sleep-wake cycle influences the level of intact parathyroid hormone in blood plasma (Chapotot et al. 1996). The level of mean intact parathyroid hormone levels significantly increased by 13% and mean intact parathyroid hormone pulse

amplitudes by 31% during sleep compared with the corresponding waking hours (Chapotot et al. 1996). Sleep-wake-dependent changes in the level of intact parathyroid hormone in the plasma suggest that sleep could be involved in the modulation of phosphate homeostatic balance.

Hypophosphatemia is considered as one of the reasons for sudden infant death syndrome (SIDS). The cause of SIDS is not yet known, but it is a sudden unexplained death of an apparently healthy baby (<1 year old), which usually occurs during sleep. It has been argued that exposure to a stressful situation, such as maternal separation, can cause enormous loss of phosphate in urine (loss of 50% of the free phosphate pool) within 24 h. The immediate drop of phosphate level also affects the diaphragm contraction, which could be the cause of sudden death (Van Kempen et al. 2013). The timing of death exhibits a temporal relationship between SIDS and sleep. Death of SIDS children usually happens after midnight (between midnight and 6:00 A.M.) (Sullivan and Barlow 2001).

It is very clear from studies that secretion of parathyroid hormone peaks during sleep in healthy subjects and, also, that hypophosphatemia and sleep are both linked with SIDS. It is not known, if (1) SIDS is also associated with an alteration in the sleep-dependent release of parathyroid hormone and/or (2) if high sleep propensity in SIDS causes hypophosphatemia because sleep deprivation induces hyperphosphatemia. Clear answers to these questions require further investigation, but altogether, studies suggest that sleep plays a crucial role in the maintenance of homeostatic balance of phosphate ions as well.

4.4.4 Role of Sleep in the Maintenance of Potassium Homeostasis

Potassium is a necessary ion involved in many physiological processes, such as regulation of acid-base balance, action potential generation, cardiovascular functioning, muscle contraction, etc. The homeostatic balance of potassium ions is also crucial because an alteration in the level of potassium affects the homeostatic balance of other ions (calcium and phosphorous ions are the best examples) (Squire et al. 2013). In addition, the transcellular potassium homeostasis balance depends mainly on acidic/alkaline nature of the medium. Acidosis in transcellular compartments induces cellular efflux of potassium from cells, resulting in hyperkalemia, whereas alkalosis stimulates an influx of potassium, resulting in hypokalemia, without a simultaneous alteration in total body potassium (Mandal 1997).

The role of sleep in the maintenance of potassium homeostatic balance can be understood by considering the changes in the levels of (i) plasma aldosterone and (ii) potassium ions in the plasma itself across sleep and wakefulness. Aldosterone hormone modulates the homeostatic balance of sodium and potassium ions. Aldosterone induces sodium and water reabsorption and potassium ion secretion in the kidney. The increased level of aldosterone reduces plasma potassium level. It has

been found that the level of aldosterone varies across sleep-wakefulness. The level of aldosterone increases during sleep and remains low during wakefulness (Charloux et al. 1999). As a result, the level of potassium should be low during sleep and high during wakefulness. Interestingly, it has been found recently that extracellular potassium levels significantly reduced during sleep and increased during wakefulness (Ding et al. 2016). Ding et al. (2016) have noticed that arousal triggers a rapid rise in extracellular potassium level, while natural sleep or anesthesia induces the opposite changes in extracellular potassium ion concentrations. Nevertheless, it is not precisely known if the reduced level of plasma potassium level during sleep is primarily because of the high level of aldosterone during sleep or its accelerated clearance during sleep by some other factors. It has also been found that the sleep-dependent shift in extracellular potassium ions is fast, compared to other ions (Ding et al. 2016), suggesting that besides the changes in the aldosterone levels across sleep and wakefulness, sleep can also be regulating the homeostatic balance of potassium level in the body.

It has also been reported that potassium ion excretion exhibits diurnal variations, and sleep deprivation alters this variation. The excretion of potassium ions remains elevated during the daytime and reduces during the nighttime. Interestingly, total sleep deprivation for the entire night period induces a significant increase in the potassium ion secretion compared to non-sleep-deprived subjects (Kamperis et al. 2010). Furthermore, it was observed that sleep deprivation did not cause any changes in the level of potassium secretion during the daytime (Kamperis et al. 2010). The increased nocturnal potassium excretion in sleep-deprived subjects suggests that sleep deprivation influences the homeostatic regulation of potassium ions in the body.

4.4.5 Role of Sleep in the Maintenance of Calcium Homeostasis

Calcium is a necessary cation and mineral of bodily electrolytes. It also takes part in the cellular signaling processes as a secondary messenger. Calcium plays an essential role in several physiological processes such as muscle contraction, blood clotting, the release of neurotransmitters from neurons, etc. (Renkema et al. 2008). The concentration of calcium in extracellular fluids is higher than intracellular fluids. In the intracellular compartment, calcium remains stored in cytoplasmic organelles like mitochondrion and endoplasmic reticulum and is released during cellular cell signaling processes (Brini et al. 2013).

There are a few studies suggesting that sleep may play a regulatory role in the maintenance of homeostatic balance of calcium ions in the body. It has been observed that in *Drosophila* brain, the level of calcium ions reduces during sleep and increases during wake conditions in the mushroom body (Bushey et al. 2015). Similar findings have also been reported in the cat (Massimini and Amzica 2001).

The extracellular calcium ion concentration progressively declines in the cortex between the onset and the offset of the depolarizing phase of the oscillatory slow waves during sleep. A significant decline (~20%) of extracellular calcium level occurs specifically during the silence periods of the cortical network during slow-wave sleep, which also significantly affects (~50% decrease) the release of neurotransmitters (Massimini and Amzica 2001).

In mammalian cells, calcium ions remain stored primarily in the endoplasmic reticulum (ER), mitochondria, and Golgi body (Barrige et al. 2003). At the cellular level, it has been found that sleep deprivation induces stress in these cell organelles (Naidoo 2009; Zhang et al. 2014). ER stress causes the changes in the levels of two endoplasmic reticulum (ER) proteins, ER-resident chaperone and immunoglobulin-binding protein (BiP), which are the prime markers of ER stress. It has been found that the level of these two proteins alters with mild sleep deprivation suggesting that sleep deprivation induces cellular stress that activates an adaptive response. The calcium cycle in the ER and mitochondria is also altered when ER remains under stress (Lautenschlaeger et al. 2012). These studies suggest that sleep deprivation may alter calcium cycle/homeostasis.

4.4.6 Role of Sleep in the Maintenance of Iron Homeostasis

Iron is one of the essential elements of life. The formation of red blood cells (RBCs) is highly dependent on iron availability and transportation of oxygen by hemoglobin. Various clinical studies have found that subjects with severe obstructive sleep apnea (OSA) had higher hematocrit levels than subjects with no OSA or mild-to-moderate OSA, which could be because of higher total RBC count to compensate oxygen deficiency (Choi et al. 2006; Feliciano et al. 2017). Further, a significant decrease in hematocrit value and total RBC count has been observed after prolonged (28 h) sleep deprivation (Goodman et al. 1990). Although, the lifespan of RBCs is roughly around 100–120 days, it is surprising that the total count of RBCs drastically reduced within 28 h of total sleep deprivation (Goodman et al. 1990). The acute decrease in total RBC count may be attributed to a phenomenon similar to sports anemia, where RBC is destroyed after running long distances. The presence of free hemoglobin and alteration in iron-binding capacity primarily contributes to sports anemia (Liu et al. 2017). Similarly, it has been reported that iron-binding capacity and plasma iron levels decline after prolonged sleep deprivation (Kuhn et al. 1967). It has also been noticed that 5 days of sleep deprivation markedly reduced the mean level of iron, diminished the absolute and relative amplitude of iron oscillations, disturbed the shape of the daily course of serum iron, and gradually decreased the period of iron rhythm in serum (Kuhn and Brodan 1982). Surprisingly, all these changes were partially restored with sleep recovery (Kuhn and Brodan 1982). These findings clearly demonstrate that inadequate sleep alters iron metabolism as well as visco-elasticity properties of the RBC.

Iron in the brain performs several essential functions such as neuronal myelination, neurotransmitter synthesis, and metabolism. The predominant cell type containing iron in the brain is the oligodendrocyte, which is responsible for the production of myelin. The alteration in the functioning of oligodendrocyte not only causes neuronal hypomyelination but also adversely affects sleep homeostasis and cognition (Beard and Connor 2003; Halassa et al. 2009). Iron also acts as a cofactor for enzymes tryptophan hydroxylase and tyrosine hydroxylase, which are involved in the synthesis of serotonin and dopamine neurotransmitters, respectively (Beard and Connor 2003). Iron deficiency or altered iron metabolism severely affects catecholaminergic neurotransmission in the brain (Beard and Connor 2003), which may in turn effect sleep regulatory systems (Madan and Jha 2012a). Melatonin increases sleep by suppressing the activity of neurons in the brain's circadian clock, and it has been observed that norepinephrine, dopamine, and serotonin influence the synthesis and release of melatonin (Mitchell and Weinshenker 2010). Therefore, imbalance in iron homeostasis or metabolism may affect sleep through both alteration in (a) the functioning of oligodendrocytes and (b) catecholaminergic-mediated synthesis and release of melatonin.

The restless leg syndrome (RLS) patients exhibit poor sleep quality along with low percent iron saturation and serum ferritin level. Interestingly, when these patients were treated with oral iron for 4–5 months, they showed a marked recovery of sleep latency and efficiency with a concomitant reduction in the number of periodic movements (Kryger et al. 2002). An abnormal iron metabolism has been noticed in patients suffering from Parkinson's disease with REM sleep behavior disorder (Hu et al. 2015). The level of transferrin significantly declines in the peripheral system in sleep-deprived subjects (Kuhn et al. 1967). Therefore, it is likely that sleep alteration in Parkinson's patients with REM sleep behavior disorder may cause an increase in the translocation of transferrin from periphery to the brain resulting in altered iron levels.

These studies clearly suggest that sleep deficit may induce homeostatic imbalance of iron in the peripheral as well as central systems. The decreased iron level in the serum and brain alters sleep, possibly by altering the functioning of oligodendrocytes and catecholaminergic-mediated synthesis and release of melatonin. Further, sleep-deprivation-mediated alterations in iron concentration, as well as its metabolism, are restored with sleep recovery, suggesting that sleep may be playing a crucial role in the maintenance of iron homeostatic balance.

4.4.7 Role of Sleep in the Maintenance of Magnesium Homeostasis

Magnesium is another most abundant mineral in our body. Half of the body's magnesium is found in the bones and the other half in cells of the remaining body organs. Many biological systems such as the muscle, nerve, heart's steady

rhythmicity, immune system, and bones essentially require magnesium for their proper functioning. Magnesium is considered to be a natural agonist and antagonist of GABA and NMDA receptors (Abbasi et al. 2012). Interestingly, it has been observed that it plays a critical role in sleep regulation as well. Murck and Steiger have found that oral administration of magnesium significantly increases the sleep EEG power within the spindle frequency range (11.0–12.9 Hz), but does not change SWS delta power throughout the night (Murck and Steiger 1998). Later, Held et al. have reported that oral administration of magnesium significantly increased slow-wave sleep as well as EEG delta and sigma power in elderly subjects (Held et al. 2002). In elderly subjects, magnesium supplement appears to improve insomnia and early morning awakening and serum melatonin concentration (Abbasi et al. 2012). Besides these, magnesium therapy has also been proposed for the treatment of periodic leg movements-related insomnia. Magnesium was orally administered to subjects suffering from insomnia related to periodic leg movements and mild-to-moderate RLS. The drug was administered in the evening over a period of 4–6 weeks. It was found that following magnesium treatment, periodic leg movement syndrome-mediated arousals decreased, and sleep efficiency improved significantly (Hornyak et al. 1998).

Sleep, on the other hand, also plays an essential role in the maintenance of magnesium level in the body. It has been found that sleep deprivation decreases mean erythrocyte magnesium concentration and intracellular magnesium level (Tanabe et al. 1997; Takase et al. 2004). Magnesium is an essential cofactor for many enzymatic reactions, especially those that are involved in energy metabolism and neurotransmitter synthesis (Morris 1992). Magnesium is very closely linked to electrolytic balance. The concentration of various other minerals like calcium and phosphate fluctuates with alterations in magnesium levels (Renkema et al. 2008). Sleep has a profound role in maintaining optimal levels of magnesium by influencing the regular pulses of aldosterone hormone in the plasma (Charloux et al. 1999; Hurwitz et al. 2004), which is responsible for regulating magnesium metabolism (Swaminathan 2003).

Elevated magnesium level in the brain upregulates NMDAR signaling and concomitantly prevents synaptic loss and memory deficit in aged rat models (Slutsky et al. 2004, 2010). Magnesium plays a crucial role in the glutamate-dependent induction of long-term potentiation (LTP) in the neurons. Prolonged membrane depolarization helps remove magnesium from glutamatergic NMDA receptors. Removal of magnesium from NMDA receptors allows calcium influx, which in turn triggers the second messenger systems to activate kinases, gene transcription, and protein synthesis (Rajadhyaksha et al. 1999; Bauer et al. 2002). The elevation of brain magnesium enhances learning and memory in young and aged rats (Slutsky et al. 2010). This elevation of brain magnesium also increases the activity of NR2B subunits of NMDAR, NMDAR signaling, and synaptic plasticity with a concomitant increase in number of presynaptic buttons in the hippocampus, which is the primary area of the brain responsible for learning and temporarily storing new information (Slutsky et al. 2010). The NMDAR-dependent induction of LTP in the hippocampus and increased synaptic efficacy after learning essentially require sleep (Madan and

Jha 2014). It is not known, however, if magnesium plays a role in the sleep-dependent induction of LTP and synaptic efficacy. Nonetheless, the level of magnesium ion changes across sleep-wake states (Ding et al. 2016). The level of free magnesium ions exhibits minor but consistent shift, with decreasing level during sleep to wake and increasing level from wake to sleep transitions in the cortical brain areas (Ding et al. 2016). Such consistent changes in the level of magnesium ions have also been observed under anesthetized conditions.

These findings suggest that (a) the homeostatic extracellular ionic regulation may be involved in the alteration of behavioral states and/or (b) changes in the ionostatic level across different behavioral states may facilitate different neuromodulators in exerting consistent and optimal changes in neuronal functions and synaptic efficacy. The implications of this phenomenon, as has been proposed, would be that this "ionostatic control" of neural activity might provide a backdrop for coordinating shifts in the behavioral state through the extensive regulation of excitability without relying on complicated receptor activation in diverse subclasses of neurons (Ding et al. 2016).

4.4.8 Role of Sleep in the Maintenance of Zinc Homeostasis

Few studies have indicated that the suboptimal level of zinc in the blood and/or brain may cause impairment in intrinsic sleep regulation and sleep quality. The subjects having an optimal zinc level and/or optimal zinc-copper ratio in the serum experienced longer sleep duration compared to the subjects having suboptimal or altered ratio (Song et al. 2012). On the other hand, subjects having a regular sleep (7–9 h per night) had the highest concentration of serum zinc compared to short (<7 h) and long (>9 h) sleepers (Zhang et al. 2009). The cross-sectional and longitudinal association between zinc status and sleep outcomes in normal school-goers has also been investigated. In a cross-sectional analysis, a significant link between zinc concentration and sleep quality in adolescence has been observed. It was found that adolescents having higher blood zinc concentrations experienced usual sleep quality (Ji and Liu 2015). Therefore, it was suggested that the likelihood of sleep disturbances in adolescents could be minimized with the increasing concentration of zinc. Surprisingly, no link was found between blood zinc level and sleep outcomes at preschool age (Ji and Liu 2015). It was, however, proposed that the lower concentrations of zinc in blood at the preschool age may be a predictor of an increased likelihood of poor sleep quality and sleep efficiency at the adolescence age (Ji and Liu 2015). Thus, it seems that the optimal level of zinc in the blood could be associated with better sleep quality.

Zinc supplementation can also improve sleep. The sleep amount in children suffering from iron deficiency anemia significantly increased with 12-month iron and zinc supplementation (Kordas et al. 2009). Not only children suffering from iron deficiency anemia but also all healthy subjects exhibited a remarkable increase in sleep amount with 60 days of triple supplementation, a combination of melatonin,

magnesium, and zinc taken before bedtime (Rondanelli et al. 2011). The indispensable effects of natural sources enriched with zinc ions, such as oysters and yeast extracts, have also been investigated. It was found that individuals treated with daily zinc supplements from natural resources for 3 months had improved sleep latency and sleep efficiency compared to control subjects (Saito et al. 2017). How zinc promotes sleep is precisely not known, but Zn remains stored and co-released from glutamatergic and glycinergic axonal terminals in the brain (Danscher and Stoltenberg 2005). Few sleep-active or sleep-promoting neurons are glycinergic in nature (Anaclet et al. 2012). Hence, it is likely that Zn may activate the glycinergic sleep-promoting neurons, which in turn may enhance sleep.

The role of sleep in the maintenance of zinc homeostasis is not known. However, psychological stress and depression reduce the level of zinc in the brain particularly in the hippocampus (Dou et al. 2014). Under normal conditions, zinc has very low permeability across the blood-brain barrier. Zinc concentration in the brain remains exceptionally stable regardless the serum concentration (Blair-West et al. 1990). Nonetheless, rapid exchange of zinc between the blood and brain takes place during the first 30 min following intravenous administration under certain situations (Pullen et al. 1990). It is also known that several stress paradigms induce a significant reduction in zinc concentration as well as alteration in the blood-brain barrier (Cieslik et al. 2011). Similarly, chronic sleep deprivation condition alters the blood-brain barrier and increases the permeability of several ions (Sharma et al. 2015). It is likely that the permeability of zinc across the blood-brain barrier increases under chronic sleep-deprived conditions, which can restore sleep as well as sleep-loss-mediated alteration in the neuronal circuitries (Cieslik et al. 2011).

4.5 Sleep and Energy Homeostasis: Regulation of Glucose Metabolism

Several papers have indicated that glucose utilization reduces during sleep. For example, plasma glucose level significantly declines after 8 h fasting while being awake, but it remains relatively constant and stable during sleep, which is also akin to fasting state (usually no food intake happens when asleep) (Simon et al. 1998). In one of the exciting studies, a link between sleep and glucose regulation was investigated. Glucose was infused continuously during sleep. This inhibits endogenous glucose production, and then the observed plasma glucose level was interpreted as changes in glucose utilization. It was observed that the levels of glucose increased during the early part of nocturnal sleep by approx. 20%, which returned to the basal level only by morning (Scheen et al. 1996). Further, these authors have noticed that with constant glucose infusion overnight, glucose level increased during NREM sleep, while it was reasonably stable during REM sleep (Scheen et al. 1996). In healthy subjects, whole-brain glucose metabolism significantly decreases during NREM sleep, and it could be one of the reasons for increased glucose levels during

NREM sleep (Nofzinger et al. 2002). In addition, it has been proposed that reduction of peripheral glucose utilization may be another cause of increased glucose level during NREM sleep (Maquet et al. 1990; Boyle et al. 1994). The propensity of REM sleep, which is an energy-consuming state, increases during the early morning. Hence, it was argued that the enhanced glucose level during sleep would fall back to the basal level during the early morning. Interestingly, the glucose level decreases during daytime sleep as well (Van Cauter et al. 1991), suggesting a modulatory role of sleep in the regulation of glucose level unrelated to the time of day.

Sleep deficit also alters glucose level profoundly. After a constant glucose infusion in non-sleep-deprived and sleep-deprived subjects, it was observed that in total sleep-deprived subjects, plasma glucose levels increased much less during the first half of the night than those getting regular sleep (Knutson 2007). During the second half of the night, glucose levels decreased under both conditions, but the decline was significantly different in sleep-deprived and non-sleep-deprived subjects (Knutson 2007). Furthermore, it was also found in that study that after sleep deprivation, plasma glucose levels were high in the midmorning to late afternoon despite similar insulin levels (Knutson 2007). Postprandial blood glucose level increases significantly in subjects suffering from chronic sleep loss as compared to subjects having normal sleep even though the insulin levels remain the same in both groups. These studies suggest that chronic or acute sleep deficit may induce some pathophysiological conditions, which may contribute to the development of glucose intolerance or diabetes.

In addition, glucose may induce sleep by exciting the sleep-promoting neurons, primarily located in the ventrolateral preoptic area (VLPO) (Saper et al. 2010). These neurons play an essential role in the induction and maintenance of NREM sleep. A rise in extracellular glucose concentration in the VLPO activates these sleep-promoting neurons as well as NREM sleep (Varin et al. 2015). It was proposed that glucose-induced neuronal excitation causes the closure of ATP-sensitive potassium (KATP) channels. Hence, the extracellular glucose can monitor the gating of KATP channels of sleep-promoting neurons, which may help the sleep-promoting VLPO neurons to change their excitability depending on the extracellular energy status. All these studies suggest that sleep and glucose homeostatic regulatory machineries are intimately linked, and an alteration in either of the two systems has a profound impact on physiology and health.

4.6 Sleep Helps in Toxin Clearance from the Body

Sleep performs several restorative functions, and one among them is a clearance of toxins or toxic metabolites. The role of sleep in metabolite clearance can be assessed primarily through two different approaches: (a) the influence of metabolites on behavioral states and (b) the production of different metabolites across different behavioral states. Some metabolites strongly influence sleep-wake states. For example, mild hypercapnia induces sleep, while strong hypercapnia induces wake state

(Fraigne et al. 2008). Supplementing 2% CO_2 in breathing air significantly increased sleep by increasing NREM sleep time and decreased sleep latency (Fraigne et al. 2008). Sleep parameters deteriorated with an inspired CO_2 of 6%. Addition of 4% CO_2 in the inspired air, however, did not produce any significant change in sleep duration. Interestingly, the breathing rate remains higher in NREM and REM sleep under mild hypercapnia compared to the normocapnia. The increased breathing rate after mild hypercapnia during sleep may help in removing excess CO_2 from the body. In addition, the breathing rate remains low during NREM sleep and increases during REM sleep under normal conditions. It is likely that REM sleep might act as a sentinel to help in maintaining the CO_2 level within physiological limits (Madan and Jha 2012a).

Neurons are highly sensitive to their environment, and changes in ionic composition in and around neurons affect their functionality. Therefore, metabolites need to be cleared intermittently from the interstitial space. The periodic clearance of these metabolites can be facilitated if the dimension of interstitial space increases from time to time. The volume of cortical interstitial space increases interestingly by more than 60% during sleep (Xie et al. 2013). Using real-time assessments of the influx of CSF tracer (Texas red-dextran, 3 kD) in awake and sleeping mice, it was noticed that periarterial and parenchymal tracer influx was reduced by ~95% in awake as compared with sleeping mice (Xie et al. 2013). Further, a radiolabeled amyloid beta protein (125I-Aβ1-40) was injected intracortically in naturally awake and sleeping mice. Brains of these animals were harvested 240 min later to analyze the retention of 125I-Aβ1-40. It was found that the clearance of exogenously applied Aβ1-40 was twofold faster in the sleeping mice as compared to the wake mice (Xie et al. 2013). The study suggests that sleep facilitates the clearance of degradation products of neural activity that accumulate during wakefulness.

A link between sleep loss with the accumulation of CSF Aβ42 in a normal aging group has also been observed. It is well known that brain's amyloid beta protein is an outcome of neuronal activity, and its level in the brain peaks during wake and falls during sleep (Beekly et al. 2007). NREM sleep duration correlates with CSF Aβ42 levels in aged subjects. Varga et al. (2016) have found a significant inverse correlation between CSF Aβ42 and NREM sleep duration and between % NREM sleep and slow-wave activity. CSF Aβ42 was not correlated with the duration of REM sleep (Varga et al. 2016). These findings demonstrate that the brain may not be in an optimal functional state during sleep deprivation to facilitate the clearance of metabolites.

Sleep possibly facilitates the clearance of biomolecules between the cerebrospinal fluid (CSF) and interstitial fluid (ISF) through convective flow to remove toxic metabolites from the brain. It was proposed that the glymphatic system is strongly stimulated by sleep, which is associated with an increase in interstitial volume (Mendelsohn and Larrick 2013). The increase in interstitial volume possibly takes place by shrinkage of astroglial cells. It is possible that sleep has a role in shrinkage of glial cells. Sleep deprivation may induce glymphatic dysfunction, which may, in turn, be involved in the pathogenesis of neurodegenerative diseases (Mendelsohn and Larrick 2013).

4.7 The Implication of Homeostatic Ionic Imbalances in Cognitive Dysfunctions

Optimal neuronal function is the outcome of their environment milieu. Therefore, any abrupt change may cause neuronal dysfunction, which may lead to pathophysiological conditions. For example, depletion of magnesium in the hippocampus seems to be a crucial pathogenic factor in the progression of Alzheimer's disease (Durlach 1990). Similarly, alteration in the mitochondrial calcium uniporter during development causes memory impairment without altering the capacity to learn. Alteration in uniporter activity during development impaired adult memory, but similar inhibition during adulthood did not affect memory (Drago and Davis 2016). Additionally, changes in the level of potassium, sodium, iron, glucose, and other ions in either the CSF or ISF profoundly induced learning deficit (Williams 2001; Hoyer 2003; Ozawa et al. 2012)

Changes in ionic concentration may induce an alkalosis or acidosis condition, which has a profound effect on cognitive ability. Alkalosis causes brain vasoconstriction, which in turn affects the processing capability of the brain and probably diminishes cognition (Farnam 2014). Antidiuretic hormone plays an essential role in the maintenance of electrolytic balances. In one of the exciting experiments, ADH injection into non-preloaded normal rats (which presumably had regular water and electrolyte balance) has no significant aversive or rewarding effect in T-maze learning experiments. However, the preloaded animals (which had an excess of either H_2O or NaCl) were motivated to learn. The H_2O-loaded animals chose the side where they could avoid the ADH microinjection, whereas the NaCl-loaded group prefers the side where they can receive ADH injection so that they can restore normal water level rapidly. The results show that ionic imbalances induce visceral learning which is mediated through the central nervous system and helps in maintaining ionic homeostasis (Miller et al. 1968).

Cellular pH or the level of hydrogen ion concentration in the body may also influence learning or cognitive ability. Elevated CO_2 levels in animals cause intense fear and panic disorder (Papp et al. 1993). In a healthy human, CO_2 produces dose-related increases in anxiety, but in patients of panic disorder, the increase in anxiety and somatic symptoms induced by 5% CO_2 exceeded those in healthy subjects (Woods et al. 1988). In the brain, H^+ can be rapidly generated by CO_2 and water, which is catalyzed by an enzyme *carbonic anhydrase*, and this proton ion causes central acidosis. It has been proposed that perhaps acidosis triggers central proton-gated currents and potentiates the feelings of panic (Wemmie et al. 2004). CO_2 also enhances the contextual fear memory retention in mice by activating acid-sensing ion channels (ASIC) (Wemmie et al. 2004). Overexpressing human ASIC1a by using the pan-neuronal synapsin-1 promoter, it has been found that transgenic overexpression of ASIC1a significantly increased neuronal acid-evoked cation currents in the amygdalar neurons. Further, they found that overexpressing ASIC1a in the amygdala enhanced fear memory (Wemmie et al. 2004).

Hydrogen ions can also act as a potential neurotransmitter (Du et al. 2014). It has been found that stimulating the presynaptic terminals increases proton concentration in synapses. Potential receptors for these presynaptically released protons are acid-sensing ion channels, Na^+-, and Ca^{2+}-permeable channels that are activated by extracellular acidosis. Interestingly, the proton-activated ASICs generate excitatory postsynaptic currents in the amygdala pyramidal neurons, and both protons and ASICs play an essential role in the induction of synaptic plasticity in lateral amygdala neurons. In fact, it is argued that based on these functions, protons are indeed neurotransmitters, which act through the postsynaptic ASICs receptor. Du et al. have established that protons (neurotransmitter) and ASICs (proton receptor) are critical for amygdala-dependent learning and memory (Du et al. 2014). The drop in pH by H+ released from neuronal vesicles in synaptic cleft enhanced the LTP in amygdalar neurons. Further, increasing the buffering capacity of the solution decreased LTP induction suggesting that drop in pH is indeed necessary for memory formation, at least in case of emotional memories (Wemmie et al. 2004; Du et al. 2014). These studies imply that proton ions can act as neurotransmitters, and this could well become an emerging field with respect to studying its functions and involvement in treating cognitive disorders.

In one recent study, it has been found that the pattern of breathing creates differential electrical activity in the human brain, which may be involved in emotional judgments and memory recall (Zelano et al. 2016). They have found that the memory recall of a fearful face was quicker during inhalation than during exhalation and suggest that the breathing phase systematically influences cognitive tasks related to the amygdala and hippocampal function. It has also been reported that learning-dependent changes in pH occur in the brain, and pH-sensitive acid-sensing ion channels are activated due to a fall in pH, which further starts a signaling cascade in neurons necessary for memory acquisition (Ziemann et al. 2009). Moreover, besides the role of CO_2 in REM sleep initiation (REM sleep helps in elimination of excess CO_2 built up during NREM sleep and ensures the acid-base balance by elevating the breathing rate), it may also help in fear memory consolidation (Popa et al. 2010; Du et al. 2014). Therefore, REM sleep could act as a bridge between the acid-base balance during sleep and memory consolidation processes. Any change in either REM sleep or acid-base homeostasis could potentially impair cognition.

4.8 Conclusions

There is definite evidence suggesting that chemoregulation and sleep are two independent systems but closely linked. Sleep disturbances either qualitatively or quantitatively alter ionic balances in the brain and body. The manifestation of different breathing rates during NREM and REM sleep and ionic imbalances in the body fluids in various sleep-related pathophysiological disorders like OSA suggest that sleep may be playing a vital role in balancing the physiological acid-base status. Endocrine system plays a central role in ionic homeostasis, and

interestingly the activity of some endocrine axis shows sleep-dependent rhythmicity. The level of some cations such as potassium, calcium, sodium, or magnesium in the brain alters during sleep and wake conditions (Ding et al. 2016). On the other hand, deficiency of these ions not only alters some vital physiological functions but also induces a significant sleep deficit. For example, magnesium deficiency in the elderly population has been shown to be the primary cause of insomnia, and oral supplementation improves sleep in such individuals (Abbasi et al. 2012). Magnesium supplementation improves insulin sensitivity in type 2 diabetic patients and also their sleep efficiency (Rodriguez-Moran and Guerrero-Romero 2003).

Neurons can only be optimally functional if their environmental milieu is adequately maintained or else it may lead to the progression of pathophysiological conditions. For example, depletion of magnesium in the hippocampus seems to be involved in the progression of Alzheimer's disease (Durlach 1990). Similarly, alteration in the mitochondrial calcium uniporter causes memory impairment. In this chapter, we have proposed that sleep plays an essential role in the maintenance of optimal acid-base balance. The influence of acute and chronic sleep loss on ionic inconsistency, however, is not known. In addition, a detail mechanism of sleep-loss-mediated alteration in acid-base dysregulation is not known. It would be intriguing to know how the ionic imbalances cause insomnia as well as cognitive deficits. Future studies may provide more insight into a close link between disruptive sleep, impaired cognition ability, and acid-base imbalances.

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