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Sleep disorders contribute to the development of dementia and Alzheimer's disease

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Abstract

Life is the highest form of adaptation to the environment which is based on energy metabolism. To maintain life, the neuromuscular system must constantly interact with the environment. The striatal muscles are the main energy consumer and their access to energy fuel is mainly limited by the brain's needs. In the state of wakefulness, the brain must continuously process streams of sensory signals and respond to them with motor actions. At the same time, the brain to be efficient must memorize the sensory-movement relationships. Brain memory networking requires additional energy allocation, and due to limited systemic energy resources, the processes of memorization are completed during the sleep phase when the inactive muscular system allows allocating the energy fuel to the brain functions such as memory trace formation and the removal of the activity-dependent waste products. Both physiological processes can be completed during sleep only, and consequently, chronic sleep disorder leads to pathological changes in brain functioning and escalation of neurodegenerative processes. Consequently, sleep disorders become the main cause of dementia which is the prodrome of Alzheimer's disease.

Keywords

Brain physiology, sleep disorders, aging, neurodegeneration

Energy metabolism of the brain

The primary goal of nervous control is the survival of the organism. This goal is achieved thanks to the body's ability to acquire, plan, and implement a variety of motor programs, including gait, voluntary movements, and food intake. Cyclic processes of food intake and digestion controlled by the nervous system provide energy and essential nutrients. Food is the major source of energy for all vital processes, motor activity, growth, and development. Under physiological conditions, the acquired energy must be optimally distributed among all organs and tissues, according to their needs for basal and activity-related metabolism. Organisms must also maintain strategic energy reserves for increased needs, e.g., fasting or excessive physical efforts and restoration of homeostasis. The latter processes include the disposal of waste

products and restoring stationary physicochemical conditions (e.g., ions concentrations, pH, temperature) in all cells and tissues.

The phenomenon of life is inextricably linked to the exchange of energy with the environment. To maintain life processes, living organisms obtain energy from the food they eat. The available energy carriers such as oxygen [1], carbohydrates [2–4], fats [5], and proteins [6] play an essential role in this process. The share of these energy carriers in maintaining life processes and homeostasis at the cellular or tissue level is quite diverse. Most organs can use any source of energy depending on the basal need, the development phase of the organism, or the level of activity. The brain is a fascinating exception in terms of energy metabolism. The functioning of the human brain is based solely on the oxidation of glucose in fairly rigidly fixed proportions: six oxygen molecules per one glucose molecule. The brain is the most energy-consuming organ in our body. Its weight of 1,400 g accounts for only 2% of the body weight and yet the brain consumes more than 60% of glucose from the blood [2]. Importantly, under physiological conditions, the blood-brain barrier is an impassable limit for other energy fuels. The exceptional dependence of the brain's energy metabolism on glucose has resulted in the fact that the level of glucose in the body is strictly controlled and within quite narrow limits. The final effect of glucose homeostasis depends on the total balance of current glucose turnover and the body's ability to store excess glucose. Both glucose deficiency (hypoglycemia) and its excess in the body (hyperglycemia) pose a threat to the functioning of the body [2, 3, 7]. Oxygen and glucose are the main sources of energy for the brain and their turnover depends mainly on neuronal activity. Under resting conditions, local cerebral blood flow is the highest in brain regions with the highest local glucose metabolism [7]. A chronic deficiency of energy which is recognized by the brain as a stressful condition imposes cortisol-dependent redistribution of energy from less important processes to the processes and tissues necessary for survival. That is why in a state of malnourishment, hormone levels that regulate tissue growth are decreased and cells become resistant to their effects.

The consumption of glucose in the human body depends primarily on the functioning of 650 skeletal muscles. With little effort, the muscles benefit from the oxidative metabolism of glucose, and in the case of higher loads, they can use non-oxidative metabolism [8]. The large mass of muscle tissue and its dependence on glucose have evolved the mechanism of selective storage of sugar in the muscles in the form of glycogen. It is estimated that in young, physically active males with a body mass of 70 kg, about 400 g of glucose is stored in striated muscles in the form of glycogen [2, 3, 7]. This is a strategic reserve and a buffer that protects the body against hypoglycemia in the event of intense exercise. The second most important glucose store is the liver [2]. Under physiological conditions, the liver stores nearly 100 g, which forms a strategic reserve for the brain and other organs, especially the kidneys and intestines. Under resting conditions (without any physical activity), fairly stable proportions of glucose distribution among the most important organs are established in the body (about 20%). To maintain metabolism in various tissues, especially in the brain, glucose must be efficiently transported and then distributed to individual organs. Under physiological conditions, the brain uses almost 60% of the glucose circulating in the blood [2, 3]. The liver, which is the main depot of glucose, releases it into the blood at a rate equal to its uptake and consumption [2, 3, 7]. When glycogen stores become critically low, the 4 g of blood glucose is protected by liver gluconeogenesis [2]. Only after extremely prolonged exercise does blood glucose fall to concentrations that result in hypoglycemia severe enough to cause neuroglycopenia [2].

Fatty acids serve as a complementary energy fuel for the human body that secures brain glucose reserves when deficient [9]. Complex and multilevel control of energy metabolism in the brain is dedicated primarily to glucose metabolism since oxidative phosphorylation in mitochondria relies exclusively on oxygen and glucose [2, 3]. The organismal energy metabolism is more diverse due to the unpredictable diet composition and capabilities of different tissues to utilize fatty acids as an energy fuel. Dietary fatty acids are absorbed from the gut and converted to triglycerides. Then lipoprotein lipase hydrolyses the triglyceride to fatty acids, which may be taken up by muscles for oxidation or adipocytes for storage [6]. Adipose tissue stores free fatty acids in the form of triglycerides, which are used as energy fuel only in conditions of energy deficit. An increase in the level of fatty acids in the blood has an inhibitory effect on glucose metabolism in the liver, which is wrongly called the "glucose-sparing effect" [10]. Such a

pathological process is observed in the case of a high-fat diet, morbid obesity, or excessive lipolysis provoked by growth hormones (GHs). In such conditions, all organs, except the brain, switch from glucose-based metabolic processes to fatty acids. At the same time, the skeletal muscles, being the main consumers of glucose, substantially reduce glucose uptake and storage. Additionally, the process of aging is accompanied by a progressive degenerative loss of skeletal muscle fibers and muscle metabolic function [11]. In these conditions, the loss of muscle fibers is combined with an increase in intermuscular adipose tissue which causes the muscles, being so far the largest consumer and storage of glucose, to rapidly lose their energy-consuming properties causing the excess glucose to remain in the bloodstream. Symptomatically, the effectiveness of insulin declines rapidly which is usually referred to as insulin resistance.

Besides skeletal muscles, an impaired free fatty acids metabolism causes lipid accumulation in the liver and heart. Accompanying aging hypoactivity potentiates sarcopenia while increasing visceral adiposity leading to chronic systemic inflammation striking even nonprotected by blood-brain barrier hypothalamic nuclei. Hypoxia and inflammation in adipose tissue is probably the major cause of the development of aging-associated diseases such as insulin resistance, type 2 diabetes, and sleep disorders [5, 12].

Under physiological conditions, the acquired energy must be optimally distributed among all organs and tissues, taking into account their resting metabolism and activity. Organisms must also maintain strategic energy reserves for increased motor activity and the post-exercise restoration of homeostasis. The latter processes include the disposal of waste products and restoring stationary physicochemical conditions (e.g., ions concentrations, pH, temperature) in all cells. Motor activity and exposure to new cognitive stimuli trigger neuroplastic changes in the brain. The hypothalamus is the major regulator that is responsible for controlling the body's internal balance. Hypothalamic control is based on the coordination of major bodily functions such as the heart rate and blood pressure, body temperature, fluid and electrolyte balance, appetite, body weight, fatigue, sleep cycle, and function of the gastrointestinal tract [13].

Energy metabolism is a multilevel- and multifactorial-controlled sequence of chemical reactions that take place in all cells and tissues of a living organism. The reactions are fueled by energy obtained from dietary intake to convert available nutrients into the molecules required for maintenance, activity, and growth. The efficiency of complex metabolic processes depends firstly on homeostasis, i.e., the steady state of internal, physical, and chemical conditions. For this purpose, the brain controls several physical-chemical parameters such as temperature, fluid balance, the pH of intra- and extra-cellular fluids, the concentrations of sodium, potassium, and calcium ions, as well as the level of blood sugar. Maintaining basal energy metabolism in the brain and muscles requires extraordinary energy expenditure. In particular, the maintenance of cellular and mitochondrial resting potentials requires maintaining the concentrations of sodium, potassium, and calcium at a certain level. The resting ionic concentrations are disturbed each time by the generated action potentials and the release of neurotransmitters in the synaptic junctions. The greater the functional activity of the nerve networks and muscles, the more disturbed cell homeostasis is the restoration which requires additional energy expenditure. This makes energy metabolism fundamental for life. An increasing body of evidence allows to posit that dysfunction of energy metabolism is the primary cause of brain aging and neurodegenerative disease [4, 14].

Feeding and sleep are behaviors fundamental to survival, and as such are subject to powerful homeostatic control [13, 15]. Based on energetic balance, the brain sets the motivational drive, which includes food intake, capability of motor activity, and even cognitive behavior. From this perspective, the energy metabolic processes are dependent on a circadian rhythm, which differentiates the level and mode of cortical activity as well as the activity of brain networks controlling the neuromuscular system. Instead, brain activity during the sleep phase is dominated by the processes aiming to restore homeostasis and remove unnecessary metabolites, especially from areas intensively stimulated during daily activity.

The neural substrates of energy allostasis

The hypothalamus lays a key role in maintaining physiological and behavioral homeostasis. In particular, the lateral hypothalamic area is the center for coordinating the sleep-wake state, food intake, energy

balance, and motivational behaviors [16]. To fulfill homeostatic/metabolic functions the hypothalamus must monitor levels of energetic and essential nutrients in the blood as well as in the cerebrospinal fluid. Towards this aim, the brain, which is tightly hidden by the blood-brain barriers, has a local incomplete barrier. Particularly, within the hypothalamus, the blood-brain barrier is not fully tight, allowing insulin, ghrelin, leptin, other peptides, and even fatty acids to penetrate the barrier and more precisely sense the nutritional value of the food consumed. The mediobasal hypothalamus, including the arcuate nucleus and median eminence, can sense fatty acids and transduce this to control food intake, thermogenesis, and intermediary metabolism [17].

A leaky blood-brain barrier increases the susceptibility of the hypothalamic nuclei to focal inflammations caused by fatty acids and, as a consequence, homeostatic and metabolic control is disturbed [18]. In particular, inflammation in the medial-basal hypothalamus results in impaired astrocyte activity and excessive activation of microglia. The resulting metabolic syndrome is characterized by uncontrolled weight gain accompanied by numerous metabolic and endocrine abnormalities, sleep disorders, and cardiovascular changes [18]. These are accompanied by attention deficit, memory impairment, and reduced impulse control constituting together the hypothalamic deficiency syndrome.

The hypothalamus as a central hormonal neuroregulator also plays an important role in the control of metabolism. The neurosecretory nuclei of the hypothalamus release hormones that regulate various aspects of the body's energy metabolism. First of all, the hypothalamus produces a thyrotropin-releasing hormone, which stimulates the anterior pituitary gland to release the thyroid-stimulating hormone (TSH) in a circadian rhythm [19]. The half-life of TSH is approximately 60 min. Particularly increased TSH activity is observed during periods of growth and development of the organism and in response to stress [19]. The main purpose of TSH is to regulate the activity of the thyroid gland, which has a significant impact on the processes of energy metabolism. Thyroid hormone—triiodothyronine (T3) by regulating the rate of glycogen degradation and gluconeogenesis affects the course of all metabolic and physiological processes in the body. Particularly, in active cells such as neurons and muscle cells, T3 increases the production of Na/K-ATPase, which allows them to maintain their membrane electrochemical gradient [20]. Finally, the thyroid hormone, acting on oligodendrocytes, regulates the processes of myelination of nerve fibers [21], and thus has a significant impact on the neuronal processes of neuronal learning that are intensified during sleep.

The neurosecretory nuclei of the hypothalamus also regulate the secretion of GH in the pituitary gland. The released GH stimulates primarily the hepatic synthesis of insulin-like growth factor 1 (IGF-1), which increases the metabolism of glucose and free fatty acids. Both GH and TSH are secreted in a pulsatile manner, with the maximum release occurring about an hour after falling asleep [22]. Consequently, sleep disorders by impairing the hormonal activity of GH and TSH have a devastating impact on all glucose-dependent physiological processes in the brain. In particular, IGF-1 and insulin share common signaling pathways and common receptors in the brain. However, due to their different half-life, their final effects are completely different. The pancreas releases insulin in response to a postprandial rise in blood glucose. Its task is to quickly lower blood sugar levels by storing glucose in the muscles, liver, and adipose tissue. Therefore, the half-life of insulin is estimated to be only 10 min. On the other hand, IGF-1, released by the GH, has a long half-life, even exceeding 15 h [21]. Therefore, the activity of IGF-1 allows for the implementation of long-term and energy-intensive processes in the nervous system, such as the proliferation of progenitor cells, their migration and differentiation, and the processes of myelination and synaptogenesis closely related to neuronal learning [21–24]. GH-dependent energy control is especially important for children's growth and development, but it also has anabolic effects in adults [24]. As a consequence, disturbances in the activity of GH and IGF-1 cause not only growth disorders of the body but also the development of many metabolic diseases, including osteoporosis, diabetes, atherosclerosis, and neurodegenerative diseases. The brain, isolated by the blood-brain barrier, is completely dependent on its lipid synthesis. In the brain, astrocytes produce lipids much more efficiently than neurons [25]. Lipids derived from astrocytes are used by neurons to create and function new synaptic connections [25]. Astrocytes also provide neurons with cholesterol, which is necessary for the formation of presynaptic vesicles used for the transport and release of neurotransmitters. As a consequence, in aging astrocytes, a

decrease in cholesterol synthesis impairs neuronal communication in the networks of the cerebral cortex [25].

The depletion of IGF-1 activity associated with sleep disorders can impair almost all metabolic processes in the brain. For example, neurons themselves are unable to synthesize neurotransmitters such as glutamate and gamma-aminobutyric acid (GABA) from glucose. In this respect, neurons and their functions depend on the glutamate/GABA-glutamine metabolic cycle in astrocytes [26]. Controlled by IGF-1, side reactions of the glycolytic pathway generate compounds necessary for neuronal function, especially glucose-derived amino acids such as serine, glycine, alanine, and glutamine, and neurotransmitters and neuromodulators, including glutamate, GABA, aspartate, d-serine, glycine, and acetylcholine. Compounds dependent on glucose and IGF-1 also include complex carbohydrates, which are components of glycolipids and glycoproteins [3].

Functional changes occurring in aging glial cells, intensified by sleep disorders, lead to complete dysregulation of energy metabolism. As a result, the balance of excitation and inhibitory processes is disturbed (glutamate-GABA balance). Consequently, a deficiency in glutamate uptake by astrocytes from synaptic clefts leads to overexcitation of glutamatergic neurons, culminating in their excitotoxic death. This, in turn, increases the activity of microglia, which are responsible for regulating the brain's response to inflammation, playing a fundamental role in maintaining homeostatic brain functions. The escalation of neurodegenerative processes caused by brain aging and failure of metabolic control leads to the complete failure of microglial activity. The consequence is numerous damage and inflammation of the nervous tissue, to which microglia are unable to respond adequately. In addition, in the process of creating neural networks, microglia are also involved in pruning unused synapses and removing apoptotic neurons [27, 28], and thus a decrease in microglial activity leads to impaired learning processes in the brain.

Short-term energy deficiency causes usually increased signaling of energy nutritional needs. In particular, norepinephrine increases arousal, and alertness thus mobilizing the brain and body for activities such as food uptake [29]. The locus coeruleus is the main noradrenergic controller [30]. Importantly, the release of noradrenaline is the lowest during sleep, rises during wakefulness, and reaches maximal levels during stress. In the latter condition, noradrenaline increases heart rate and blood pressure, elevates glucose uptake from energy stores, and intensifies the blood supply to skeletal muscle. In the brain, noradrenaline improves attention and enhances the formation and retrieval of memory traces. It is an important homeostatic controller of the body which receives afferents from the lateral hypothalamus while sending projections among others to the thalamic relay nuclei and the cortex, which may switch the brain mode from sleep to wakefulness [30]. It seems that here a triggering factor can be a decreased level of glucose in the blood that cannot be supplemented by hepatic glycogenolysis.

Brain aging results in many quantitative and qualitative modifications in its functioning. Especially, the reduction of synaptic connections and plasticity, causing massive neuronal death, and progressing cortical atrophy are accompanied by behavioral and physiological changes including hormonal and metabolic ones [31]. Particularly, sleep, and cognition are highly disrupted by these pathological changes. Consequently, many older adults suffer from primary sleep disorders, such as insomnia and sleep-disordered breathing, excessive daytime sleepiness, circadian rhythm disorders, and rapid eye movement (REM) sleep behavior disorders [32]. All of them impair the brain's energy metabolism.

Sleep and wakefulness—two physiological modes of the brain's activity

The alternating phases of sleep and wakefulness have always aroused the interest of scientists. Research results collected over the last century have identified the most important brain centers involved in the control of sleep and wakefulness [29]. Their activity and contribution to the alternation of wakefulness and sleep cycles remain incompletely understood. It seems very tempting and logical to confront the wakefulness-sleep cycle with energy metabolism and the maintenance of brain energy homeostasis.

Feeding and sleep are behaviors fundamental to survival, and as such are subject to powerful homeostatic control [13, 15]. Based on energetic balance, the brain sets the motivational drive, which includes food intake, the capability of motor activity, and even cognitive behavior [6]. From this

perspective, the energy metabolic processes are dependent on a circadian rhythm, which differentiates the level and mode of cortical activity as well as the activity of brain networks controlling the neuromuscular system. Instead, brain activity during the sleep phase is dominated by the processes aiming to restore homeostasis and remove unnecessary metabolites, especially from areas intensively stimulated during daily activity. Additional energy resources are allocated for the plastic transformation of neuronal networks, including memory trace formation.

Wakefulness is necessary for consciousness, and impaired wakefulness is a symptom of many diseases [29]. Consciousness is central to the human experience, and wakefulness is a necessary prerequisite for consciousness. Considering the brain as a movement controller, we treat it as a complex transducer of sensory signals into specific signals used to control the operation of skeletal muscles. The brain cortex participates in all aspects of planning and implementation of movements and the acquisition (learning) of new movement programs. Efficient motor control is due to the central representation of the body's own body and the external environment. Both these cortical representations are polymodal and are formed based on signals coming from various sensory organs. Motor activity and exposure to new cognitive stimuli trigger neuroplastic changes in the brain. Human conscious life activity involves almost all areas of the brain, from the entire cerebral cortex, limbic system, and basal ganglia, to the cerebellum and spinal cord. Thus conscious activity is responsible for the very high level of brain metabolism during the waking period, which usually is elevated by the high energy consumption of muscular activity. Many hours of vital activity in the brain lead to a disturbance in the homeostasis of accumulation of waste products, manifested by a feeling of fatigue. The primary physiological aim of sleep is to restore homeostasis and the physicochemical conditions, necessary for the proper functioning of the nervous system.

The formation of memory traces in the brain networks and their preservation requires extraordinary energy inputs which cause neuroplastic processes to be usually separated from daily brain activity and realized during sleep. Plastic processes during wake are biased towards synaptic potentiation, resulting in a net increase in synaptic strength in many brain circuits [33]. Such increased synaptic weight would be unsustainable in the long run, due to increased demand for energy, space, supplies, and the risk of synaptic saturation. Sleep is important to renormalize synaptic strength to a baseline level that is sustainable and beneficial for memory and performance [33]. The quality of sleep decreases as we age and disruption of the regular sleep structure is a frequent antecedent to the onset of dementia in neurodegenerative diseases [31, 34].

Most repairs and plastic changes in the brain take place during sleep and what is more important, they mostly depend on the release and activity of the second organismal energy controller, i.e., GH. The largest GH peak occurs about an hour after the onset of sleep [21]. IGF-1 is a hormone similar in molecular structure to insulin. Both IGFs and insulin exert a variety of bioactivities that mainly increase anabolism. Insulin shows short-term effects contributing to glucose fuel energy storage in striatal muscles, liver, and adipose tissue. In contrast, IGF activity is responsible for long-term physiological processes determining cell fate such as cell proliferation, differentiation, and inhibiting apoptosis.

The process of neuronal plasticity can be also characterized by the myelination of neuronal fibers [22]. This is the first critical point in brain development from which declining the brain undergoes plastic changes throughout life and only their nature, level, and intensity are adjusted to our cognitive and motor activity [22]. The decreasing vital activity of the elderly causes a progressive degradation of the brain structures and thus the vital functions of the human brain. The decreasing vital activity of the elderly causes a progressive degradation of the brain structures and thus the vital functions of the human brain.

Sleep and waste product clearance

Depending on the phase of the brain's life, each long-lasting functional disturbance in the metabolism of neuronal networks places its neurons on the path of programmed death. The escalation of this process results firstly in a gradual decline in the activity of brain functional networks. The decline, in turn, lowers the energy metabolism that triggers the vicious circle of neurodegeneration and massive death of neurons and glia. The brain is equipped with an autonomous immune defense system that allows removing dead

cells. Microglia penetrating all spaces of the brain recognize and efficiently neutralize and remove both pathogens and pruned axonal fibers, and debris of dead cells. Infections, inflammations, dysfunctions, and apoptosis are signaled to the microglia by several chemoattractants, the simplest of which are potassium ions released in the event of loss of tightness of the axonal myelin sheaths or the process of apoptosis [9]. The efficiency and effectiveness of the microglia depend on the speed of transmitting the threat signals (both inflammatory and necrotic) and the speed of movement of the microglia. Both of these factors are determined by the speed at which the cerebrospinal fluid moves into the intercellular spaces. Moreover, the limited population of microglia and extensive and scattered inflammatory and necrotic foci in the aging brain, may slow down and eventually completely block microglial activity. In the process of neurodegeneration, the massive death of neurons reaches the critical point where the microglia are unable to cope with the excess of dead neurons. Additionally, the massive death of neurons impairs the metabolism of other neurons and glial cells within networks directing them to the necrotic and apoptotic pathways, which ultimately terminates the functioning of brain cognitive and plastic processes. The damaged and dying neurons will never recover, but likely the brain can regain some lost function through neuroplasticity. Its multimodal and greatly redundant neuronal networks can modify their structure and remap to other areas of the body to take over function, compensating for damaged networks. An intensive cognitive metabolism combined with rich physical activity ensures the development and maintenance of the brain networks in better shape until a late age. Therefore brain involution symptoms such as sleep disturbance appear later and neurodegenerative disorders progress more slowly. This opens a window of opportunity to treat or slow down the process of brain neurodegeneration before it reaches the critical turning point.

In the brain life activity, sleep plays an important regenerative role. First of all, it ensures the restoration of homeostasis in the brain disturbed during wakefulness. In the sleep phase, unnecessary metabolic products that accumulate during wakefulness are removed from the brain [34, 35]. The cleaning process also includes the removal of dead neurons and their redundant synaptic connections. The leading role in the process of brain cleansing is played by the so-called glymphatic system. It is a macroscopic brain waste disposal system that uses a network of perivascular channels formed by astroglial cells. Interstitial solutes, including protein waste, are removed from the brain via meningeal and cervical lymphatic vessels [34].

Sleep has a critical function in ensuring the brain's metabolic homeostasis [35]. The restorative function of sleep is attributed to the enhanced removal of potentially neurotoxic waste products that accumulate in the awake brain. The glymphatic system returns excess interstitial proteins to the general circulation for degradation in the liver. The cerebrospinal fluid rinses the brain, and throughout interchange with interstitial fluid removes interstitial proteins, including β-amyloid. The activity of the glymphatic system is based on its dependence on astrocytic aquaporin-4 (AQP4) water channels. Its function is homologous to peripheral lymphatic removal of interstitial metabolic byproducts.

During sleep, the throughput of the glymphatic system increases, allowing for the effective removal of soluble proteins and metabolites from the brain [34]. In the sleep phase, it increases the interstitial volume in the brain by nearly 60%, thus accelerating the cleansing process twice [35]. Sleep allows the brain to drain freely, and sleep disorders that develop with age impair the cleansing functions of the glymphatic system. The discovery of sleep-dependent glymphatic drainage and its dysfunction-induced protein aggregation shed new light on the pathogenesis of many neurodegenerative diseases. Therefore, the aging-related dysfunctions of the glymphatic system constitute a new therapeutic target in the prevention of neurodegenerative diseases.

Importantly, sleep disturbances cause a temporary failure of brain clearing, the effects of which can be long-lasting. Failure to remove waste products cannot be fully compensated by another sleep [36]. Therefore, insomnia and sleep disorders negatively affect human life by limiting cognitive functions, attention control, memory, and learning, and suppressing emotional reactivity [36]. Thus, chronic sleep disorders are a major risk factor for neurodegenerative diseases, especially Alzheimer's disease (AD) [36, 37].

So far, several brain regions involved in the control of sleep and wakefulness and the functioning of the glymphatic system have been identified. The main centers include the brainstem, hypothalamus, and basal forebrain [38]. Neurons active during sleep have been found in several subregions of the hypothalamus [38]. In particular, the ventrolateral preoptic area is a key region to promote non-REM (NREM) sleep. In the aging process, the death of neurons controlling sleep mechanisms is observed, especially those in the suprachiasmatic nucleus of the hypothalamus [36]. The locus coeruleus isa noradrenergic center that sends broad projections to multiple brain areas and plays a pivotal role in regulating the transitions of vigilance states as well as a wide array of arousal-associated behaviors, such as attention, cognition, and orientation [16].

The flux of the cerebral-spinal fluid is at least in part enforced by arterial pulses. Consequently, in the awake brain, a decreased interstitial space increases resistance and limits cerebrospinal fluid drainage. The transition to NREM sleep augments the volume of the interstitial space and therefore the efficiency of glymphatic solute clearance [35]. Waste removal is the most efficient in the early hours of sleep [34]. The senescent brain spends, however, less time in NREM sleep, causing a decline in the clearance of brain waste [34]. This, in turn, intensifies the course of neurodegenerative processes that ultimately close the vicious circle of brain self-destruction.

Accumulation of β-amyloid deposits results in cerebrospinal fluid clearance continuing to decline [34]. The β-amyloid seeding begins across cortical brain areas characterized by the highest synaptic activities [34]. The amyloid plaque growth is associated with an inflammatory response, involving reactive micro- and astrogliosis [34]. Consequently, the cumulation of age-related decline in cerebrospinal fluid production, the decrease in perivascular AQP4 polarization, gliosis, and plaque formation all critically impede glymphatic flow and finally disarrange waste clearance [34]. The increased incidence of aggregation-related disorders seen with aging depends on both vascular health and glymphatic patency [34]. Deterioration of the vascular bed leads to progressive demyelination and deterioration of all cortical brain functions. Brain aging is associated with microangiopathy, suggesting that elderly individuals may also impair the metabolic activation of cerebral blood flow that escalates inflammatory processes [39, 40]. Resultant hypoxia-ischemia brain injury is characterized by a pronounced inflammatory response along with structural alterations in the blood-brain barrier followed by energy deprivation [4], and the release of reactive oxygen species [39, 40].

The impact of sleep disorders on the pathogenesis of neurodegenerative processes

In a healthy brain, processes controlling energy metabolism, oxidative stress, and proteostasis are fully efficient allowing avoidance of dysfunctions leading to extensive neuronal death that opens a vicious circle of neurodegenerative disease [41]. Even low-level but long-sustaining disturbances in the metabolism of neuronal networks may place their neurons on the path of programmed death [42]. The escalation of this process results firstly in a gradual decline in the activity of the neuronal functional networks. The decline, in turn, lowers the energy metabolism that triggers the vicious circle of brain aging and neurodegeneration [42]. The first and most relevant for brain aging are energy metabolism-related changes autonomic disturbances, deficient glucose metabolism, and hypertension [4]. They are followed by sleep disorders, olfactory dysfunction, and psychiatric symptoms [37]. Particularly, sleep disturbances escalate brain dysfunctions.

Sleep disorders such as insomnia or excessive sleepiness are common in the elderly. There are also disturbances in REM activity patterns. These problems may be associated with progressive damage to the brain structures controlling sleep and wakefulness, circadian rhythm disorders, and motor behavior [43, 44]. Circadian rhythm disorders and poor quality of sleep intensify pathophysiological changes in the brain [45]. In particular, neurodegenerative changes in the control areas in the brainstem and the neighboring regions may negatively affect the activity of the centers regulating sleep and wakefulness [45].

Importantly, sleep disorders seem to intensify neurodegenerative processes [46–48]. Impaired waste product removal causes inflammation in the brain and abnormal protein homeostasis. Currently, it is believed that neurodegenerative diseases such as Huntington's disease [46] and AD [48] may develop as a result of these pathologies. Sleep disorders lead to deficits in cognitive, attention control, and processing speed. As a result, affective disorders such as impulsiveness and emotional liability develop [46].

Sleep disorders are a basic component of mild cognitive impairment and AD [31, 48, 49]. Sleep disorders in AD are characterized by an increasing decrease in the slow-wave activity of the brain and a significant shortening of the REM phase [31]. Sleep disorders are associated with impaired activity of neurons in the cerebral cortex and thus may accelerate neurodegenerative processes. In the brain, there is a very strong relationship between the activity of neurons and trophic processes. Decreased neuronal activity promotes not only the accumulation of β-amyloid and phosphorylated tau protein [31] but also impairs all processes related to energy metabolism [4, 45]. Physiological, metabolic, and behavioral changes associated with aging, as well as increased susceptibility to environmental factors, increase the risk of primary disorders of systemic metabolism, manifested, among others, by sleep disorders [31].

Sleep disorders are also common in patients with Parkinson's disease (PD) [32, 50]. Daytime sleepiness and fatigue are common problems in this group of patients. Poor quality sleep causes an increased feeling of fatigue during the day, which is associated with the failure to restore brain homeostasis. However, in PD the main problem in brain metabolism can be associated with deficient neurogenesis which is responsible for motor learning and maintaining motor memory [51].

The alternating cycle of sleep and wakefulness guarantees the full efficiency of processes dependent on the circadian rhythm. The cognitive processes and motor behaviors characteristic of the awake state cause disturbances in brain homeostasis, which requires longer repair processes to restore [4, 50]. Therefore, switching off from interaction with the environment during sleep allows for the effective restoration of homeostasis and consolidation of information obtained during wakefulness in the structure of the brain [50].

In this context, it has been noted that sleep disturbances occur in patients with multiple sclerosis and are strongly associated with the most common and disabling symptom of the disease, i.e., fatigue. It is estimated that fatigue occurs in 90% of patients [52]. This symptom intensifies with the passing of the day [52]. It seems that the feeling of fatigue may be an indicator of the insufficiency of central metabolic processes, provoking the transition of the brain from wakefulness to sleep.

Abbreviations

AD: Alzheimer's disease

GABA: gamma-aminobutyric acid

GHs: growth hormones

IGF-1: insulin-like growth factor 1

NREM: non-rapid eye movement

REM: rapid eye movement

TSH: thyroid-stimulating hormone

Declarations

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The author declares that he has no conflict of interest.

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