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MELATONIN, PINEAL GLAND AND SLEEP DISORDERS: FROM THEORY TO PRACTICE

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ABSTRACT

The article discusses the physiology of sleep and mechanisms of sleep disorders. Possible therapeutic solutions to treat sleep disorders can be provided through functional and holistic biological medicine, which employs a number of device-based treatments, stem cells and therapy with pineal gland cell extracts.

KEYWORDS: Pineal gland, sleep, sleep disorders, insomnia, stem cells.

The conundrum of sleep has always drawn special attention not only as a biological process but also due to its psychological and even mystical peculiarities. Albeit the complete biological purpose of sleep is yet to be uncovered, to this date, we managed to understand some of its mechanisms and observe the effects of sleep disturbances on health and quality of life. Similar to many other biological processes sleep has a cyclic nature. This phenomenon has a name of circadian rhythm and it applies in particular to the change of wakefulness and sleep, which under normal conditions is characterized by relative stereotyping, but may be disrupted, for instance, in long-distance flights with time zone changes or in connection with work associated with periodic night duty, as well as by chronic stress, diseases and the intake of various medications.

Sleep is a functional state characterised by changes of the state of consciousness and bodily movements that at any stage can be interrupted by physical stimuli. A regular person spends about a third of his life sleeping. Sleep arises from the influence of somnogenic mechanisms, tonic systems of the cerebral cortex, subcortical formations and reticular substance. Therefore sleep disturbances can arise due to pathological disturbances at any level.[1,2]

Changes in the level of wakefulness (i.e. anxiety, lethargy, asthenia, etc.), as well as sleep disorders (from insomnia to hypersomnia and the whole range of other intermediate and relevant disarrays), can have a very significant effect on the person's activity, ability to work, general health and mental state. Albeit having a great significance in maintaining a good quality of life sleep disorder rarely reaches the level when it becomes a dangerous condition. However, a rough estimate is that nearly half of the global population does nevertheless suffer from some form of sleep disorder.[1-3] In some severe cases, which are relatively uncommon, substantial sleep deprivation leads to severe mental disorders, intolerable torture incompatible with life that as an extreme manifestation can be well illustrated by central hypoventilation syndrome a.k.a. Ondine's curse.

Driven by both homeostatic and circadian mechanisms sleep consists of five stages – four stages of a slow wave sleep, a.k.a. Non-REM sleep (non-rapid eye movement), and fast wave sleep – REM sleep (rapid eye movement). If the onset of slow wave sleep is associated with neuropeptides and increased "sleep drive", then a fast sleep is associated with the frontal cortex inhibition and disinhibition of the limbic system. Sleep is associated with effects of various hormones, which may stimulate the onset of sleep via GABA and melatonin receptors or act as modulators of wakefulness and REM sleep via choline, epinephrine, dopamine, histamine, and serotonin systems.[1-5]

PHYSIOLOGY AND NEUROENDOCRINE MECHANISMS OF SLEEP REGULATION

Physiological duration of sleep in healthy individuals varies according to their age. The need for a longer sleep is greater in children and subsequently decreases towards old age. Normally human adult's need for sleep varies from 5 to 10 hours a day, averaging at 6-8 hours. The quality of sleep and its duration largely depend on the person's well-being and the general state of health, mood, physical and mental activities.

Normally, when falling asleep, slow wave sleep starts first, during which a subsequent change of its stages (from I to IV) takes place followed by a fast wave sleep. The duration of each of these cycles (6-8 per night) during the night sleep can fluctuate. The duration of slow

wave sleep in an adult is normally 75-80% of the entire period of night sleep. During the slow wave sleep, such vital signs as blood pressure, heart and respiratory rates and body temperature tend to decrease. During the slow wave sleep muscle tone is preserved, the sleeping person tends to change the pose, and fast eye movements are absent.[1,7]

REM-sleep, a.k.a. paradoxical phase of sleep is characterised by rapid eye movements and loss of muscle tone (except the outer eye muscles and some nasopharyngeal muscles)**.** When suddenly awakened during a fast wave sleep most people remember bright, often emotionally charged dreams.[1,7,8]

The phase of fast sleep changes slowly 90-100 minutes after the onset of sleep, and in an adult, it makes 20-25% of the total duration of sleep. During a fast sleep thermoregulatory mechanisms are inhibited, and although respiratory centre reacts to the concentration of CO_2 in the blood, respiration sometimes becomes irregular. Irregularity and fluctuations are observed in blood pressure and pulse rate as well.[1,7,8]

The slow/fast sleep ratio changes with age. In newborns, fast sleep takes approximately half of the time. Later the duration of fast sleep gradually decreases. The transition between wakefulness and sleep, as well as the change in phases of sleep, depending on the reticular formation activity.[9]

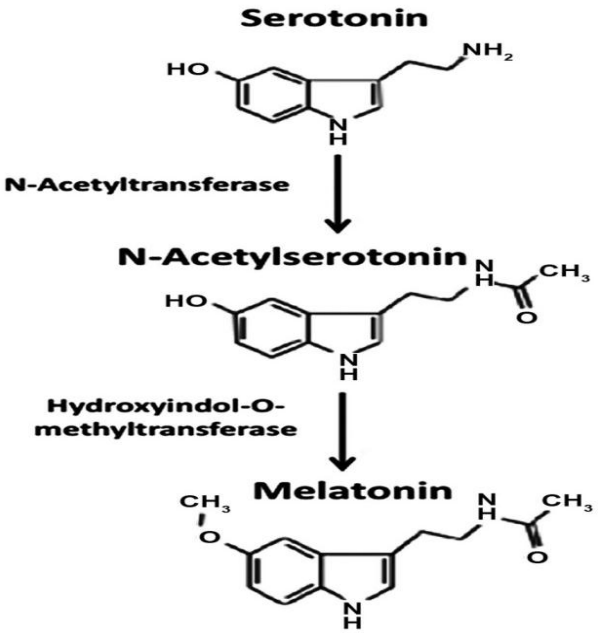
Sleep is governed by the parasympathetic nervous system, so erections occurring during sleep are used for differentiation between psychological (functional) and organic impotence, since in case of organic impotence there is no erection occurring even in sleep.

There is a growth hormone secretion (STH) increase during the first two hours of sleep. Peak levels of STH are observed in the III and IV stages of slow wave sleep (during the delta sleep period). At the same time, the production of cortisol decreases while prolactin secretion increases. The release of ACTH and cortisol increases towards the end of sleep, closer to awakening.[6,10]

Shortly before awakening, precursors of the end of sleep gradually appear: the sleeping person changes position more often, body temperature increases to the baseline value, and the concentration of corticosteroids decreases.

Epiphysis or pineal gland - the endocrine gland of a neurogenic group, is a size of a pea organ located in the region of the quadrangular medulla. The pineal gland is the main source of melatonin – a biochemical regulator of the circadian rhythm. In humans, up to 80% of melatonin is produced in the pineal gland. Retinal exposure to light inhibits melatonin synthesis, while darkness triggers melatonin production.[11]

Melatonin (N-acetyl-5-hydroxytryptamine) is an indolic derivative of serotonin, which synthesis is catalysed by enzymes N-acetyltransferase and hydroxyindole-O-methyltransferase. Structurally melatonin is close to serotonin, N, N-dimethyltryptamine, 5-methoxy-N, N-dimethyltryptamine, and other similar chemical compounds widely present in animal and plant kingdoms.[29] Human adults produce about 30 μg of melatonin per day and its concentration in serum at night is 30 times greater than during the day. Melatonin is transported bound to serum albumin. After melatonin is released from albumin, it binds to specific receptors on the membrane of target cells, penetrates the nucleus where it performs its action. Melatonin is rapidly hydrolysed in the liver and excreted in the urine. The main melatonin's metabolite is 6-hydroxymelatonin sulfate, the content of which allows you to judge the production of melatonin by the pineal gland indirectly.



Graph 1: Biosynthesis of melatonin.

Melatonin secretion is subject to the diurnal rhythm, which, in turn, determines the rhythm of gonadotropic effects and sexual function.[6,10] The synthesis and secretion of melatonin depend on the illumination - an excess of light reduces its formation, and a decrease in illumination increases the synthesis and secretion of the hormone. A person with a regular daily routine and sleeping at night has about 70% of the 24-hours melatonin production occurring during the night. It was established in a clinical setting that sleep deprivation leads to disruption of the 24-hours melatonin production - the production at night decreases and approaches the day-time level of production.

The effect of light on the pineal gland is carried out through the nerve pathways that make up the photoneuroendocrine system. The main light signal goes through the retinohypothalamic pathway that starts from the retinal photosensitive cells and reaches the

suprachiasmatic nucleus of the hypothalamus. Other pathways i.e. geniculohypothalamic and serotonergic tracts indirectly modulate the activity of the suprachiasmatic pacemakers. Signals from the suprachiasmatic nuclei, which vary by the circadian rhythm, are transmitted to the paraventricular nucleus of the hypothalamus, and from there as part of the intermediolateral column of the spinal cord reach the upper cervical ganglion. Sympathetic postganglionic noradrenergic fibres innervate melatonin-secreting cells in the pineal gland. Noradrenaline's action on postsynaptic β1 and α1-adrenergic receptors of pineal gland trigger melatonin synthesis. The excitation of the suprachiasmatic nucleus causes inhibition of norepinephrine release in upper cervical node neurons that respectively reduces melatonin secretion.[12-17]

The activity of pineal gland and amount of melatonin it makes gradually reduces with age. The reduction of melatonin production contributes to the development of insomnia. Melatonin supplementation may help to ameliorate insomnia. Disturbances in the circadian rhythm such as jet lag, night shifts, etc. are associated with decreased melatonin production.[24]

The sleeping state is characterised by periodic dreams - illusory phenomena that arise during sleep, which can be of varying degrees of brightness and complexity. Indeed, the content of dreams is influenced by the current, usually inadequately evaluated information, entering the brain from extero- and interoceptors exposed to influences during sleep. However, the nature of dreams is somewhat predisposed by previous events and thought processes. According to Hobson's activation-synthesis model, dreams are produced by chaotic bottom-up activation of sensorial cortex in the brainstem during REM sleep, activation of the visual cortex, and secondary interpretation and synthesizing by mnemonic and higher-order frontal areas.[17,23]

In addition, the sleeping person does not only see dreams but also emotionally reacts to their content, which is sometimes manifested by motor reactions and effects on the emotional state of a person upon awakening.

At this point, we should mention neurohormone oxytocin, which is known to be responsible for emotional bonding, social interactions, and empathy and so on. Apart from that, there is strong evidence that oxytocin influences sleep. Levels of oxytocin peak during REM sleep. Oxytocin levels are also correlated with slow wave sleep. Dreams from the 2nd stage of slow wave sleep and further through REM sleep are filled with social communications. Oxytocinergic activity is regulated by the paraventricular nucleus in the hypothalamus, which is in close proximity to centres that regulate arousal and sleep-wake states.[27] As for the possible (and totally plausible as a matter of fact) link between endogenous N,N-dimethyltryptamine (which is found in abundance in plant kingdom, an extremely widely spread neuromodulator in many animals and an "ancestral neuromodulator", according to Andrew R. Gallimore, PhD) and sleep, we would abstain from touching this topic in this paper until more data is available.[29]

Dreams manifest mainly during the fast phase of sleep, which completes each of its cycles and during the night it is usually repeated several times. Upon awakening from the slow phase of sleep, as a rule, traces of the dream are not stored in memory, but it is recognized that memorable nightmares can be associated with the slow phase of sleep; in such cases the awakening is sometimes accompanied by a state of temporary disorientation or even fear.[25,26,28]

BIOLOGICAL EFFECTS OF MELATONIN

Melatonin neutralizes the damaging effects of oxidative stress. Its antioxidant potential is manifested through the ability to bind to free radicals including hydroxyl radicals formed during lipid peroxidation and exogenous carcinogens. It also activates glutathione peroxidase - a factor protecting the body from free radical damage. Said make melatonin the most powerful endogenous scavenger of free radicals. In recent years, there has been evidence that melatonin can be located not only in plasma but also in cell nuclei and protect the macromolecules of the nucleus from oxidative damage in all subcellular compartments.[18,19]

In the early stages of embryonic development biogenic amines including melatonin play the role of specialised cellular signalling molecules that regulate cell renewal processes. It has been established that melatonin can suppress cell proliferation with the strength of its effect being not inferior to colchicine - a powerful cytotoxic agent. In a number of studies on laboratory animals and in tumour tissue cultures it was found that melatonin has an oncostatic effect. The mechanisms of action of melatonin on tumour growth are diverse: it affects the synthesis and secretion of pituitary and sex hormones, modulates the immune response in the presence of tumour cells and has a direct cytotoxic effect. There are suggestions that melatonin may enhance the expression of adhesion molecules and thus inhibit tumour growth since it is known that in most malignant tumours there are abnormalities in cell adhesion and defects in intercellular connections.[20-22]

The melatonin can attenuate the proliferating cell nuclear antigen (PCNA) - a reliable marker of proliferative activity of tumour cells. Under the influence of melatonin, in some forms of cancer (breast, ovary, prostate, etc.), a decrease in the proliferative capacity of cells was observed, and the number of cancer cells entering the apoptosis is increased (oncostatic effect).[21-23]

In vitro, melatonin suppressed the growth of melanoma cells. Although the effect of the hormone depended on the intensity of tumour proliferation, the tumour growth

was inhibited in lesions with moderate but not with high proliferative cell activity. The effects of melatonin are dose-dependent, and the exact mechanism of oncostatic action remains not completely clear. Epidemiological data show that women working on night shifts, aviation employees (flight attendants, dispatchers), radio and telegraph operators, have an increased risk of developing breast cancer, while women who are primarily blind (i.e., deprived of light) have this risk two times less.[21-23,51]

Experimental data, as well as clinical observations, give a notion that pineal gland and melatonin that it produces are involved in the body's defence systems against non-specific stressors. In case of prolonged stressful stimuli, a two-phase reaction is observed: the initial decline in epiphyseal activity during the resistant phase of stress with its further sharp rise. In experiments on rats, it was shown that melatonin is capable of changing the negative emotional state and reducing anxiety. According to numerous observations, the hormone stabilises the activity of various endocrine systems disorganised by stress, including eliminating excessive stress-related adrenal hypercorticism. However, it is necessary to mention that oversupply of melatonin may cause symptoms of depression.[23]

An important consequence of prolonged stress is immunodeficiency. Melatonin contributes to the normalisation of immunological parameters.

Melatonin and other epiphyseal hormones can be classified as geroprotective. The relationship between the degree of age-related involution of the pineal gland and the decrepitude of tissues was established. It is known that during ageing the degree of immunological protection decreases, and melatonin, as it has been repeatedly stated, has immunomodulating activity. Melatonin participates in the regulation of the thymic function that results in increased T-cells' and phagocytes' activity.[30]

Various experimental data shows that lack of melatonin contributes to faster ageing, earlier onset of menopause, obesity, development of cancer and insulin resistance, and accumulated free radical cell damage.

SLEEP DISORDERS

In some patients with insomnia or hypersomnia, disturbances in the distribution of sleep time during the day are more pronounced than those of sleep itself. Such disorders can be endogenous and have an organic nature due to the internal defect of the driver of the circadian rhythm (suprachiasmatic nucleus of the hypothalamus) or exogenous (associated with the environment) due to the disintegration of incoming stimuli. With such disorders, it may be necessary to examine patients under the conditions of the "day-night" cycle. Transient sleep disorders that can occur in many patients include the long awakening syndrome (60 million people/year) and sleep disorders associated with shift work. The syndrome of late falling asleep is characterised by a late onset of sleep and late awakening, but the absence of sleep disorders. There is a violation of the regime in which the actual onset of sleep comes about 3 hours after the individual would attempt to fall asleep. With the syndrome of early sleep, which is usually observed in the elderly, patients describe excessive drowsiness, which usually starts in the evening hours and early awakening that starts from 3 to 5 am.[1,2]

As criteria of normal sleep, the following should be applied:

- Rapid immersion in a dream (for 10-15 minutes).
- Continuity of sleep, without prolonged awakenings: normally there are small awakenings to roll over, to change the pose from leaking muscles. Normally, these awakenings are short-lived, and the person does not remember them.
- Healthy sleep is characterised by a sufficient duration and ensuring the quality of life: feelings of vivacity, restoration of strength and energy.

The International Association of Sleep Research Centers has developed a classification of sleep and wakefulness disorders, based on the characteristics of their clinical manifestations.

It is based on four groups of syndromes:
1) disorders of sleep and sleep duration (dyssomnia or insomnia);
2) excessive duration of sleep (hypersomnia);
3) disorders of the sleep-wake cycle;
4) various disorders associated with sleep or awakening.

Later A.M. Wayne and K. Hecht published their own more detailed clinical classification based on this document.

I. Insomnia

1) psychophysiological:
a. temporary, situationally conditioned,
b. constant, situationally conditioned;
2) with neuroses;
3) with endogenous mental illness;
4) abuse of psychotropic drugs and alcohol;
5) under the influence of other toxic factors;
6) with endocrine-metabolic diseases;
7) with organic brain diseases;
8) with diseases of internal organs;
9) due to syndromes that occur during sleep:
a. sleep apnea (respiratory arrest),
b. motor disorders in sleep (nocturnal myoclonus, restless legs syndrome, etc.);
10) caused by a change in the usual sleep-wake cycle;
11) constitutionally conditioned shortening of the duration of sleep.

II. Hypersomnia

1) paroxysmal:
a) narcolepsy,

b) Pickwick syndrome,
c) Klein-Levine's syndrome,
d) hypersomnia in the picture of paroxysmal conditions associated with other diseases,
e) periodic hibernation syndrome;
2) permanent:
a) idiopathic hypersomnia syndrome,
b) psychophysiological hypersomnia:
i. a temporary, situationally conditioned,
ii. a constant,
c) with neuroses,
d) when taking psychotropic drugs and other toxic effects,
e) with endocrine-metabolic diseases,
f) for organic diseases;
3) due to syndromes that occur during sleep:
a) sleep apnea,
b) motor disorders in sleep (nocturnal myoclonus, restless leg syndrome, etc.),
4) caused by a change in the habitual rhythm of sleep-wakefulness;
5) constitutionally conditioned lengthened night's sleep.

III. Parasomnias

1) motor:
a. somnambulism,
b. speaking in a dream,
c. bruxism,
d. changing the position of the head in a dream,
e. myoclonus of legs,
f. nocturnal "paralysis";
2) mental:
a) nightmares,
b) awesome dreams,
c) the phenomenon of "intoxication" from sleep;
3) vegetative:
a) nocturnal enuresis,
b) respiratory (apnea, asthma, sudden death syndrome),
c) cardiovascular (cardiac arrhythmias),
d) headaches,
e) gastroenterological (gastroesophageal reflex);
4) associated with a change in humoral regulation:
a) paroxysmal hemoglobinuria,
b) familial hypokalemic periodic paralysis;
5) epileptic seizures associated with sleep.

INSOMNIA

Insomnia (dyssomnia) - in practice it is rather correct to treat insomnia as dissatisfaction with sleep. According to ICD-10, the main diagnostic criteria of insomnia are: 1) poor quality of sleep; 2) frequency of sleep disorders at least 3 times a week for at least 1 month; 3) concern about insomnia and its consequences, both at night and during the day; 4) pronounced distress or an obstacle to social and professional functioning due to unsatisfactory duration and/or quality of sleep.

Insomnia can be presumed (in the form of disturbed sleep), intermittent or transitory (frequent awakenings) and post-somnolence (early awakening followed by inability to continue to sleep, usually accompanied by a feeling of discomfort, weakness, fatigue, etc). In addition, transient insomnia may last for several days (due to the move or extreme situations), short-term insomnia lasting from several days to 3 weeks (due to illness, situational neurotic reaction), and chronic insomnia often associated with chronic physical illness or with a primary sleep disorder. Intrinsically sleep disorders can be caused by dysfunction of the limbic-reticular system.[34]

In a practically healthy person (from the point of view of a neuropathologist and a psychiatrist) the temporary sleep disorders (violation of the duration of sleep, sleep and wakefulness formulas) may be caused by unmet needs (thirst, hunger, etc.), disparity of quality and quantity of food and/or medications. Transitory changes in the quality of sleep or shortening of its duration can be associated with uncontrolled pain, pruritus, nocturia and emotional distress.[31]

Sleep disorders can be triggered by a violation of sleep and wakefulness (night time shifts, frequent long-distance flights with the intersection of time zones, etc.). A disorganised, constantly changing the schedule of sleep-wakefulness is often associated with irritability, affective disorders, and at times even with sociopathic behaviour.

Frequently the origins of circadian rhythm’s disturbances root in the emotional sphere, the state of distress, and situational neurosis. At the same time disturbance of the sleep-wakefulness regulation affects the characteristics of the person's emotional status, can lead to the development of negative emotions, contribute to the advance of neurotic reactions, and hinder optimal professional activity. Patients suffering from insomnia often worry or even fear that they are not able to fall asleep and that sequentially leads to a sleep disorder. Thus, a particularly vicious circle is created: neurotic reactions provoke insomnia; insomnia leads to expansion of the neurotic disorders, the growth of their severity and the development of even more pronounced sleep disorders.[33]

Patients with functional insomnia often resort to the use of sleeping pills, alcohol and other substances, which often results in adverse outcomes. Insomnia associated with alcohol and drug intake (in particular antidepressants, psychostimulants, diuretics, antiepileptic drugs, beta-blockers, xanthine derivatives, nicotine, caffeine) and insomnia arising in connection with the cessation of drug intake (primarily sedatives and hypnotics) are called exogenous.

There is a rare form of primary idiopathic insomnia that may have a familial trait. This form of insomnia starts to manifest itself in childhood or youth and persists throughout life. It is characterised by a relatively short,

fragmented sleep, increased fatigue during the day and often irritability and depression.

HYPERSOMNIA

Hypersomnia (somnolence) is described as pathological drowsiness, excessive yawning, and overwhelming desire to sleep occurring during the day time. A person can fall asleep while working, eating or driving a car. The total sleep time per day is usually significantly higher than normal. It is important, from a practitioner's point of view, to distinguish hypersomnia from pronounced asthenia or depression.

Temporary hypersomnia can be the result of prolonged sleep deprivation or intake of medications (tranquillizers, neuroleptics, antihistamines, hypotensive drugs, etc.). The cause of persistent hypersomnia may be associated with somatic diseases like hypothyroidism, chronic liver or kidney failure.

Another distinct form of hypersomnia is narcolepsy. Narcolepsy is characterised by occasional short-term attacks of insurmountable sleep, provoked by either inactivity or stereotyped activity (driving, working on machinery, etc.). Narcolepsy manifests itself more often at the age of 15-25 years, but its debut may happen in a much wider age range - from 5 to 60 years. Attacks of narcolepsy last about 15 minutes and individuals usually wake up during a phase of rapid (paradoxical) sleep. During the narcolepsy attacks the hypnagogic hallucinations decreased muscle tone or repetitive stereotyped movements without reacting to external stimuli may occur. Upon waking up individuals feel refreshed, reinvigorated and the effect lasts for about 2 hours. Later between attacks patients become sluggish and lose their attention. Their night sleep is usually disturbed by frequent awakenings and accompanied by parasomnia.[32]

Cataplexy is the phenomenon of falling asleep and awakening during which patients with preserved orientation are not able to speak or move. In 80% of cases, narcolepsy is combined with attacks of cataplexy. This combination confirms the conditionality of hypersomnia attacks with narcolepsy and allows not resorting to additional examinations of patients.[52]

Essential narcolepsy frequently combines with cataplexy (Lowenfeld-Henneberg syndrome), which manifests as a short-term (not more than 1-2 min) immobility due to a sudden loss of muscle tone. Individuals with Lowenfeld-Henneberg syndrome manifest jaw drop, head falling on the chest, weakness in legs, etc. However, the onset of cataplexy is often limited only to the sagging of the lower jaw and head, loss of speech, weakness in limbs.[32,35]

Hypersomnia can be related to neurosis. In such cases, it is associated with drowsiness and sleep attacks during the day in the absence of sleep disorder at night. Often hypersomnia is combined with mental disorders, in particular with depression. Sometimes patients themselves establish a connection between falling asleep at the wrong time and unpleasant experiences or anxiety. Unlike narcolepsy with functional hypersomnia, attacks of daytime sleep are not combined with paroxysms of motor disorders like cataplexy; there are neither manifestations of "sleep paralysis" nor hypnagogic hallucinations.[37]

Staying in a state resembling a normal dream during the day is called lethargy. The syndrome of lethargic sleep (periodic hibernation syndrome) is a consequence of the disturbance of the awakening mechanisms of the reticular formation in the mesencephalic-diencephalic area of the brain. It is manifested by periodic attacks of insuperable sleep lasting from several hours to 2-4 weeks. Sleep is accompanied by muscle hypotension, tendon hyporeflexia or areflexia, arterial hypotension, and lack of control over the pelvic organs' function.[38-42]

The Pickwick syndrome is primarily manifested by pronounced sleepiness in the daytime, obesity, as well as hypoventilation, cardiopulmonary syndrome, polycythemia and fascicular twitching. The syndrome was described by A. Auchingross and colleagues in 1955, and in 1956 M. Burwell proposed to call it "Pickwick" after the character from the novel by Charles Dickens "Posthumous notes of the Pickwick Club" whose description being "red-faced, obese, drowsy" corresponded to the description of this syndrome.

Persistent episodic hypersomnia with cognitive and mood changes comprise Klein-Levin syndrome. Emerging bouts of sleep last from several days to several weeks. Upon awakening patients usually experience unusual hunger (bulimia), unstable mood (dysphoria), motor anxiety, increased sexual activity, decreased muscle tone, hallucinations, disorientation, memory loss. It occurs more often in adolescents or young males. The origin of the Klein-Levine syndrome is unknown. Sometimes it occurs after the encephalitis or craniocerebral trauma. It is assumed that the emergence of Klein-Levine syndrome is due to the impaired functions of the hypothalamic and limbic structures[43-46]. The syndrome was described by the German neuropathologist W. Kleine and the English physician M. Levin.

PARASOMNIA

Parasomnias include abnormal episodic conditions that occur during sleep: sleepwalking, sleepwalking, night terrors, nightmarish dreams, nighttime cardiac rhythm disorders, hypnotic myoclonic twitching, congenital central hypoventilation syndrome, teeth grinding (bruxism), etc. Their origin is mainly psychogenic.[36]

The most striking manifestation of parasomnia is somnambulism - sleepwalking (from Latin *somnus* - sleep + *ambulare* - to walk). It is more common in

children and young individuals. Usually, it is combined with night fears, concoction. It occurs during the first third of the night sleep under the influence of external stimuli (moonlight, table lamp, etc.). However it can occur spontaneously. While sleepwalking patients perform automated complex actions: get out of bed, say something, try to go somewhere, at times even commit health or life-threatening actions, while retaining the functions of sensory systems and movement coordination that allows them to overcome dangerous situations. It requires considerable effort to wake up such person. Somnambulistic episodes develop during a period of slow sleep and usually last up to 15 minutes, and it takes a considerable effort to wake a sleepwalker up. Somnambulism is often observed in emotional and hypersensitive individuals. It is considered to be a manifestation of neurosis and even psychopathy.[47,48,62]

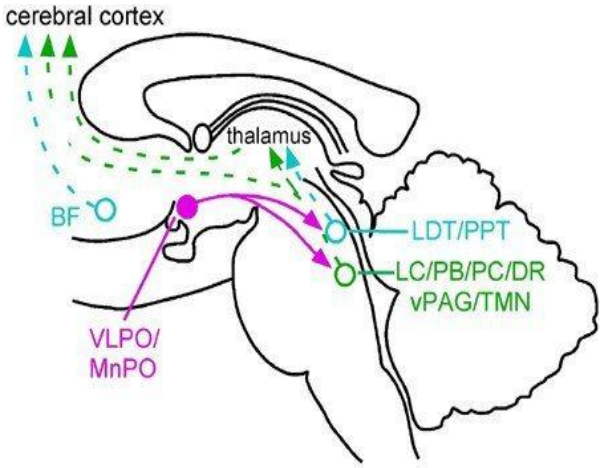
MORPHOLOGICAL BACKGROUND FOR SLEEP DISORDERS

Serotonergic neurons of the raphe nuclei are playing an important role in the process of falling asleep. If this system is damaged or the pharmacological blockade of serotonin occurs, complete or partial insomnia may occur.[60,61]

GABA-ergic system of ventrolateral preoptic nucleus (VLPO) is the main brain's inhibitory system that keeps the wake centres off. Electrical stimulation of this area by the current of any frequency invariably causes sleep.[57]

The ascending reticular activating system (ARAS), also known as the extrathalamic control modulatory system or the reticular activating system (RAS) described by Italian neurophysiologist Giuseppe Moruzzi in 1961. It is a network of nuclei located in the brainstem, pons Varolii, medulla, and hypothalamus.

Nonspecific thalamic nuclei is an "open the gate" for the flow of sensory information to the cortex during wakefulness and "close" them down during sleep. The irritation of these nuclei by the low-frequency current synchronises the potentials of the brain stimulating its descent into sleep. Sleep that occurs as a result of irritation of these nuclei is indistinguishable from normal physiological sleep.[2,4]



Graph 2. During the sleep, VLPO inhibits the wakefulness centres. Legend: LTD / PPT - cholinergic pathways of the laterodorsal tegmentum / pedunculopontine nucleus; BF - cholinergic projections of the basal part of the forebrain; LC / PB / PC / DR - glutamatergic and monoaminergic projections of the blue spot / parabrachial core / sub-spot / suture nuclei; vPAG / TMN - glutamatergic and histaminergic near-conductor gray matter / tubero-mammillary nucleus; VLPO / MnPO - GABAergic ventrolateral preoptic region / median preoptic nucleus. (Source: Saper et al., Neuron., 2011).

Diagnostic Tools For Sleep Disorders

The most common method of studying sleep disorders is polysomnography. This examination is conducted in a special laboratory where individual should spend the night. During sleep, many sensors simultaneously record the bioelectric activity of the brain (EEG), cardiac activity (ECG), respiratory movements of the chest and anterior abdominal wall, inhaled and exhaled airflow, blood oxygen saturation, etc. Such survey enables studying of the brain activity and functioning of the main body systems during each of the five stages of sleep that, in its turn, helps to identify abnormalities and to find out the cause of sleep disturbance.

Another method of diagnosing sleep disorders is to investigate the average sleep onset latency (SOL). It is used to identify the cause of drowsiness and plays an important role in the diagnosis of narcolepsy. The study consists of five attempts to fall asleep, which are carried out during waking hours. Each attempt lasts 20 minutes with the interval between attempts being 2 hours. The SOL more than 10 minutes is considered to be the norm, from 10 to 5 minutes - borderline, less than 5 minutes - pathological sleepiness.

TREATMENT STRATEGIES FOR SLEEP DISORDERS

Treatment of sleep disorders depends on the etiological factors causing it. In the case of somatic pathology, treatment should target underlying disease. It is also necessary to avoid the factors triggering sleep disorder.[49,50,53-56] For that purpose some simple rules

should be observed: 1) try to adhere to the sleep-wakefulness regime with a sufficient amount of sleep, which varies largely individually and normally changes with age; 2) maintain the quiet environment in a darkened, well-ventilated bedroom; bed should be comfortable, but not too soft; 3) avoid abundant food, coffee, alcohol, smoking, emotional stress at least 3 hours before sleep; 4) instead recommend some calming activity before going to bed (i.e. reading, knitting, etc.), a short-term walk, warm bath, etc.

In case if sleep disorders are caused by somatic diseases (i.e. lung, heart or gastrointestinal pathology, i.e. bronchial asthma, angina, thyrotoxicosis, peptic ulcer, etc.).[58,59]

Traditionally public's approach to management of insomnia would be an administration (often self-administration) of hypnotic drugs although their side effects can be quite significant (dizziness, memory loss, confusion, etc.). It has been recognised that sleeping pills affect not only the state of sleep but also disturbs cognitive function, tends to accumulate in the blood, affect the level of wakefulness during the day, reduce attention and level of mental alertness. All this implicates the need to resort to the use of hypnotic pharmacological drugs only when its necessity is absolutely justified.[63-69]

Prolonged intake of tranquillizers and sleeping pills, in addition to its direct effect, causes depletion of the brain's reserves of serotonin and norepinephrine that carries detrimental effects on cognitive function and psycho-emotional status. VLPO is activated by substances that cause sleep (serotonin, adenosine and GABA) but is inhibited by mediators that support wakefulness (norepinephrine and acetylcholine).

Transcranial electrostimulation

Transcranial electrostimulation - the effect on brain stem structures with small amplitude pulses (up to 3mA) with a rectangular bipolar asymmetric pulse shape. Transcranial electrostimulation is a method of neurotherapy that is used for treatment and prevention of depression, neuroses, insomnia, addictions, for pain control purposes.

The principle of therapeutic effect of transcranial stimulation is based on activation of brain alpha-rhythms and modulation of brain electrical activity pertinent to physiological sleep, increase of the concentration of serotonin, acetylcholine, met-enkephalin and beta-endorphins. There is an effect on the subcortical structures of the brain by microcurrents through special electrodes.

Transcranial electrostimulation is an effective alternative to medications, especially in conditions requiring long sessions of psychotherapy. During the session, there is a pleasant feeling of relaxation, lightness in the body, clarity of thoughts. Transcranial stimulation is usually carried out in concurrence with psychotherapy an, at times, medicinal treatment.

Activation of alpha brain rhythms (in the range of 8-12 Hz) leads to a state of relaxation, which reduces stress, normalises the mood, and regulates the perception of various types of pain.

Microcurrents of complex sequence activate specific groups of neurons that are located in the brain stem. These groups of nerve cells produce serotonin and acetylcholine, which affect the chemical activity. By changing the electrical and chemical activity of certain neurons in the brain stem, this procedure regulates the activity of neurochemical brain systems. As a result, the brain produces electrical activity of a certain type, known as the alpha state, which can be measured by recording the EEG (frequency 8-13 Hz). Alpha rhythms are accompanied by a sense of calm, relaxation and stimulate mindfulness.

Transcranial micropolarization of the brain allows you to activate parts of the brain without external intervention. This technique provides an opportunity to investigate the excitability of neurons in the cerebral cortex and the consistency of the functions of its individual parts.

Among the other additional effects of transcranial electrostimulation are:

- The decrease in the severity of neurotic symptoms, the removal of tension, feelings of anxiety, various fears.
- The emotional background acquires a positive colour.
- During the session, the patient experiences a state of rest, muscle relaxation (muscle clips are removed).
- Due to the regulation of the processes of excitation and inhibition, the affective tension is removed, on the one hand, and the inhibition (depressive state), on the other.
- Unlocking the mechanisms of psychological defence.
- The effect of analgesia, which allows relieving pain symptoms with concomitant somatic diseases (myalgia, cardialgia, neuralgia, headaches of various origin).

Electrobiosleep

Rectangular pulsed currents of low frequency and low power have proved themselves in the treatment of patients with some diseases in the pathogenesis of which functional disorders of the nervous system predominate. The treatment is carried out from the Biosleep at a pulse frequency of 10 Hz; the current strength is from 2 to 2.5 mA, the duration of the procedure is 30 minutes, every other day, for 10-15 procedures.

After the procedure is over and the device is turned off patients continue to sleep for another 30 minutes - 1 hour. A deep refreshing sleep, similar to physiologic

sleep, promotes a good state of health. The electrical resistance contributes to the restoration of the impaired function of the central nervous system and higher vegetative-endocrine centres. It also has a mild hypotensive effect and normalises cardiac rhythm.

Phototherapy

If the circadian rhythm is disturbed, phototherapy is a good effect, since stimulation of hypothalamic nuclei responsible for the synthesis of melatonin occurs through the optical receptors. Phototherapy should be performed in a hospital environment since the essence of treatment is that a person is exposed to either sunlight or bright white light from artificial sources with certain wavelengths. As a source of illumination the light-emitting diodes, lasers, fluorescent lamps, dichroic lamps or very bright light having a full spectrum of daylight can be used. The optimal time of phototherapy is determined individually depending on the features of the sleep disorder of the individual patient.

The effect of phototherapy is aimed at the resynchronisation of biological clocks and the long-term adjustment of the required time for falling asleep and awakening. In order to achieve the effect, the session should be conducted as early as possible after a spontaneous (late) or early (forced) awakening of a person. Besides, phototherapy is effective in a number of skin diseases, arterial hypertension, migraine, pain syndrome, mental disorders and seasonal depression.

Darsonvalization

Darsonvalization is a therapeutic method in which pulsed high-frequency currents of low strength are used, safe for humans. Under the influence of these currents, the following processes occur in the tissues:

- metabolism acceleration;
- vasodilation;
- improves blood and lymph circulation;
- promotes faster dissolve of hematomas;
- anti-inflammatory effect.

Darsonval consists of a generator of high-frequency impulse currents and glass electrodes through which these currents are conducted to the body. Local darsonvalization is usually conducted using two methods: contact and non-contact. Darsonvalization of the head is used for metabolic disorders, insomnia, hypertension, hair loss, neurosis, migraine.

CELL THERAPY IN MANAGEMENT OF SLEEP DISORDERS

Functionally, many cells producing melatonin belong to the so-called diffuse neuroendocrine system - the universal system of adaptation and maintenance of homeostasis of the body. Within this system, two links of melatonin-producing cells are distinguished:

- central (includes the pineal gland and cells of the visual system), in which the melatonin secretion rhythm coincides with the light-dark rhythm;
- peripheral - all other cells, where the secretion of the hormone does not depend on light.

The amount of hormone that is produced in the pineal gland is not enough to ensure the numerous biological effects of melatonin. Studies have shown that after removal of the pineal gland in experimental animals significant amounts of melatonin are detected in the blood. At present, it has been firmly established that the pineal gland is not the monopoly organ of melatonin production.

As the pineal gland is not the monopoly organ of melatonin production the stem cell therapy of chronic sleep disorder target most important organs and enfolds as many of them as possible depending on exact case to stimulate the own melatonin production. The cells of the pineal gland produce peptides to correct and enhance the gland function.

As a part of a treatment paradigm for hypersomnia stem cell therapy primarily targets systemic disorders triggered by dysfunction of the liver, kidneys, adrenal cortex (in case of hypocorticoidism), pancreas, hypothalamus, thyroid (hypothyroidism), thymus (acute and chronic infections) and many others.

Stem cells maximally naturally affect the pineal gland by restoring the production of their own melatonin in the body in the quantity and frequency that is genetically programmed - no other drug is capable of that! This ensures a high efficiency of Stem cells, the complete absence of side effects and the ability to combine it with any therapy.

It was demonstrated by multiple studies and observations that even though immediate period after stem cell implantation may be associated with either excessive sleepiness or, on the contrary, hyperactivity, difficulty falling asleep and a certain level of non-restorative sleep, within 2 weeks post-implantation most of the patients experience reinstatement of normal sleep pattern.

Let us further analyse the possible mechanisms of transitory sleep disorders occurring during initial stages post implantation and contemplate on mechanisms of beneficial therapeutic effect of stem cells on the sleep.

Needless to say, that stem cell treatment, as any medical procedure, inevitably is a stressful experience, especially for patients with underlying psychological distress, including both depression and anxiety. It is well known that depression and anxiety are associated with disrupted sleep; hence the transitory sleep disorders post stem cell implantation is entirely justified. It is also accepted as the fact that the extent of baseline psychological distress, including symptoms of anxiety and depression, is directly linked to the level of sleep disorders.

Another reason for transitory sleep disorders may be a short-term inflammatory reaction few days after stem cell implantation mediated by cytokines and interleukins. However, shortly after the initial period of pro-inflammatory reaction the actual anti-inflammatory effect of stem cells, modulated via secretion of anti-inflammatory factors, is triggered that greatly contributes to restoration of good quality sleep.

Stem cells play a pivotal role in the development of a protective and reparative homeostatic response in obstructive sleep apnea, particularly concerning its cardiovascular consequences. The potential interactions between the obstructive sleep apnea co-morbidities that are associated with cardiovascular risk (i.e. obesity, metabolic syndrome, hypertension, diabetes) and their effects on the protective and reparative mechanisms of stem cells should also be considered as a powerful therapeutic tool.

PEPTIDES AND CELL EXTRACTS IN MANAGEMENT OF SLEEP DISORDERS

Peptides are tiny informational molecules made up by amino acids that directly impact the genes function. Different tissues produce peptides involving into protein metabolism. Their principal task is to initiate DNA scanning and as a consequence they activate the production of protein by appropriate cells and monitor their further correct work. It was discovered that the shortage of peptides would provoke disturbance on cells operation, rapid ageing of tissues, appearance and aggravation of pathological processes.

Both experimental research data and clinical observations demonstrated the beneficial effect of naturally occurring peptides extracted from stem cells' culture on maintenance of biological homeostasis in ageing individuals who are otherwise considered healthy as well as in individuals with chronic systemic and acute conditions. It was indicated that peptides contribute to the management of cell function, embedded in the proteins process of metabolism and even restore the cell functions.

The pineal gland contains a wide range of factors and peptides, which in turn produce peptides that are responsible for the normal function of pineal gland cells. The protein molecules of pineal gland tissue consist of many organic compounds that are essential constituents of living cells.

The major role of pineal gland peptides is to trigger the transcription of information from the DNA code in the cells of the pineal gland. Peptides modulate the normal function of the pineal gland to operate as required by nature in youthful cells. The abnormal work of pineal gland peptides will resume to different disturbances of the endocrine system. Consequently, sufficient presence of pineal gland peptides is the absolute need for normal endocrine function.

The positive effect of exogenous administration of pineal gland peptides/cell extracts was demonstrated in multiple clinical studies over the decades. It has been established that exogenous pineal cell extracts act as a potent anti-inflammatory and anti-oxidative stress agents, moderate endogenous production of pineal hormones and neuromodulators that ultimately results in a massive anti-ageing effect, contribute to the normalization of endocrine function, and stabilise sleep pattern in a very rapid manner.[30]

It was demonstrated in an experimental model that pineal-gland peptides have immunomodulatory, anxiolytic, antioxidant properties and their high bioavailability can be achieved even with intranasal administration.[71] It was also noticed that pineal-gland peptides have a positive effect on reproductive cycles of the observed animals.[70] The prospective mechanisms of action can be attributed to modulation of electrical activity of cells of the pineal gland and to the ability of pineal-gland cell extracts to stimulate syntheses of other hormones and neurotransmitters, like oxytocin and many others.[70-72]

The pineal gland is producing a number of monoamine neurotransmitters - indolamines. A tryptophan nonapeptide delta-sleep-inducing peptide, which is produced in the pineal gland, is influencing the secretion of indolamines. A delta-sleep-inducing peptide of the pineal gland is stimulating melatonin, 5-methoxytryptophol and serotonin synthesis and release. These effects do not occur through the noradrenergic or opioidergic systems and do not appear to activate one of the adenylate-cyclase-linked receptors, and its exact mechanism of action is remaining unclear.[73]

Another interesting fact worth giving attention is that Alzheimer's disease patients show impaired melatonin production and altered expression of the 2 G protein-coupled melatonin receptors MT1 and MT2. The role of amyloid β peptides in dysfunction of the melatonergic system has been established. Hence, restoring the pineal gland functional activity and rescuing receptors function may be of therapeutic value in the management of patients with Alzheimer's disease.[72]

Pineal gland cell extracts are available in two forms: as nanomized peptides and as "Mito Organelles" cell extracts (SBI, Germany). The former one, known as Nano Organo Peptides (NOP), is suitable for parenteral administration and for sublingual. Due to its small molecular linear size and a molecular weight less than 10 kDa, it has the capacity to be easily absorbed in the oral mucosa. Such way of administration allows active ingredients to escape the first pass metabolism and is non-invasive in the same time. The recommended dose and frequency of administration of NOP is one vial every alternate day.

As for "Mito Organelles" pineal extracts, its molecular weight is somewhat higher than in NOP, ranging between 45 to 65 kDa. It makes the route of administration either subcutaneous or intramuscular. However, the higher concentration allows reducing the frequency of administration to 2 times per week. Both types of pineal cell extracts have supreme bioavailability and outstanding efficacy. In most of the cases of chronic insomnia, it is possible to see positive dynamics in quality of sleep two weeks after the beginning of therapy. Both products are well tolerated by recipients, and adverse reactions are anecdotal.

Conflict of interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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