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Bakalářská práce

Cirkadiánní systém a neuropsychiatrická onemocnění

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Poděkování

Ráda bych poděkovala své školitelce PharmDr. Aleně Sumové, DSc. za pomoc při psaní této práce, čas, který mi věnovala, a za trpělivost. Mé díky patří také všem členům oddělení neurohumorálních regulací Fyziologického ústavu AV ČR za jejich vřelé přijetí a v neposlední řadě Lumírovi.

Prohlašuji, že jsem tuto bakalářskou práci vypracovala samostatně a s použitím uvedených pramenů.

Abstrakt

Neurodegenerativní a psychiatrická onemocnění jsou významným problémem, týkajícím se veliké části lidské populace. V poslední době vzrůstá povědomí o poruchách spánku a cirkadiánních rytmů, které tyto nemoci často doprovázejí a jež byly dříve spíše opomíjeny. I přes neznámou příčinu mají tato narušení funkce cirkadiánních hodin devastující dopad jak na pacienta, tak často i na jeho pečovatele. Díky dnešním znalostem molekulárního fungování cirkadiánních hodin a pokročilým metodám je možné u neuropsychiatrických onemocnění studovat jak výstupní rytmy fyziologických funkcí, tak i stav centrálního pacemakeru. Množství dat shrnutých v této práci naznačuje významnou roli poruch cirkadiánních hodin u pacientů trpících neuropsychiatrickými onemocněními, a v některých případech dává podklad pro snahy o vývoj nových terapeutických postupů. Ty by měly sloužit především ke zkvalitnění života pacientů prostřednictvím zlepšení fungování jejich cirkadiánních hodin.

Klíčová slova: neuropsychiatrické onemocnění, cirkadiánní systém, člověk, melatonin, hodinový gen

Abstract

Neurodegenerative and psychiatric disorders are an important issue, affecting a great part of our population. Recently, awareness of sleep disturbances and circadian rhythm dysfunctions accompanying these diseases is growing. Although the cause of circadian clock malfunctions in neuropsychiatric disorders remains to be elucidated, they have a destructive impact on quality of life of both patients and their caregivers. Thanks to our knowledge on molecular mechanisms of the circadian clock and novel techniques, it becomes possible to study the state of the central pacemaker, as well as its' output rhythms. This thesis provides a summary of data suggesting an important role of circadian system malfunctions in patients suffering from neurodegenerative and psychiatric diseases. In some cases, these data also suggest new therapeutic approaches, which could in the future help to ameliorate the patients' quality of life, by improving the functioning of their circadian system.

Key words: neuropsychiatric disease, circadian system, human, melatonin, clock gene

List of Abbreviations

3xTg	triple transgenic
ACTH	adrenocorticotrophic hormone
AD	Alzheimer‘s disease
ALS	Amyotrophic lateral sclerosis
APP	amyloid precursor protein
ARC	arcuate nucleus
ARNT	aryl hydrocarbon receptor nuclear translocator
AVP	arginine vasopressin
Aβ	amyloid β
BMAL1	brain and muscle ARNT-like 1
BNST	bed nucleus of the stria terminalis
BPD	bipolar disorder
CLOCK	circadian locomotor output cycles kaput
CRY	cryptochrome
Cry1	cryptochrome gene 1
Cry2	cryptochrome gene 2
DLMO	dim light melatonin onset
DMH	dorsomedial hypothalamus
EDS	excessive daytime sleepiness
EEG	electroencephalography
EKG	electrocardiography
EMG	electromyography
EOG	electrooculography
FFI	fatal familial insomnia
GABA	γ-aminobutyric acid
GHT	geniculo-hypothalamic tract
GRP	gastrin releasing peptide
HD	Huntington’s disease
IGL	intergeniculate leaflet
LS	lateral septum
MnPO	median preoptic nucleus
mRNA	messenger ribonucleic acid
MT1	melatonin receptor type 1
Npas2	neuronal PAS domain-containing protein 2 gene
NREM	non-REM
OCD	obsessive/compulsive disorder
PAS	Period-Arntl-Single-minded
PD	Parkinson’s disease
PER	Period protein
Per1	Period gene 1
Per2	Period gene 2
PGO	ponto-geniculo-occipital
PLMS	periodic limb movement disorder
PVN	paraventricular nucleus
qPCR	quantitative polymerase chain reaction
REM	rapid eye movement
RHT	retinohypothalamic tract
RORa	RAR-related orphan receptor alpha

SAD	seasonal affective disorder
SCN	suprachiasmatic nucleus
SDB	sleep disordered breathing
SLD	sublaterodorsal nucleus
SNAP-25	synaptosomal-associated protein 25
SNP	single nucleotide polymorphism
SOD1	superoxide dismutase 1
SWS	slow wave sleep
VIP	vasoactive intestinal peptide
VLPO	ventrolateral preoptic nucleus
VTA	ventral tegmental area

Table of Contents

1. Introduction

Circadian system is an important part of the field of physiology and its correct functioning allows organisms to anticipate daily changes in the environment and adapt their behavior and physiological processes to these exogenous cycles. Many processes taking place in our body are under the control of the circadian system, including sleep-wake cycle, locomotor activity, body temperature and levels of many circulating hormones, and therefore, when the circadian system becomes disrupted, the consequences can be devastating. It has already been known for some time that disruption of daily behavioral and sleep patterns is associated with certain neuropsychiatric disorders. Recently, more neurodegenerative and psychiatric disorders have been found to present with some kind of circadian disruption and numerous studies are aiming to uncover the underlying cause of this comorbidity. Growing knowledge of the molecular mechanism underlying the circadian clock and rapidly evolving scientific methods allow us now to study not only the overt output rhythms of physiological processes, but also the clockwork of the circadian system itself.

The aim of this thesis is to provide an overview of neuropsychiatric disorders linked to disruptions of the circadian system and offer a summary of dysfunctional circadian rhythms found in these diseases. Two disorders, one representing the neurodegenerative disorders and one the psychiatric disease, will be covered in detail and finally, the gathered data will be discussed.

2. Regulation of sleep and wakefulness

2.1. State of wakefulness and wake-promoting neuronal networks

Waking is defined as a state of the body characterized by behavioral arousal, cortical activation apparent on electroencephalograms (EEGs), and high activity of postural muscles apparent on electromyograms (EMGs).

The waking state is maintained by multiple neuronal systems using different neurotransmitters. The crucial network for maintenance of cortical activity and behavioral arousal is the ascending activating system located at the junction of the rostral pons and caudal midbrain [1]. It consists mainly of monoaminergic and cholinergic neurons [2] projecting to the thalamus, basal forebrain and cerebral cortex [3]–[6]. Another area of the brain contributing to maintaining the wakefulness is the lateral hypothalamus. Its neurons contain the neurotransmitters called orexins or hypocretins, receive afferent innervations from the ascending arousal system [7] and project to the cerebral cortex, brainstem and basal forebrain [8]. Activity of the lateral hypothalamic area also participates in the wake-promoting processes [9], [10]

2.2. State of sleep and sleep-promoting neuronal networks

Sleep is characterized by a behavioral state of reversible perceptual disengagement from and unresponsiveness to the environment [11]. It is a vital part of our lives, affecting our energy conservation [12], cognitive functions [13]–[15] or immune system (Bryant, 2004). The importance of sleep can be demonstrated on the case of fatal familial insomnia (FFI), a very rare prion disease causing complete inability to sleep, leading to dementia and death [16]. Based on EEG, sleep consists of two main states which cyclically alternate during the period of sleep, namely rapid eye movement (REM) sleep and non-REM (NREM) sleep [17]. NREM sleep is accompanied by variable, yet synchronous cortical EEG including sleep spindles, K-complexes and slow waves, low muscle tonus and minimal psychological activity [18]. The NREM sleep state can be divided into 4 progressively deepening phases. The 4th phase, also called the slow wave sleep (SWS), is the deepest sleep, with slow, high amplitude EEG activity in the delta range [19]. REM sleep on the other hand is characterized by fast desynchronized EEG activity, complete atonia in postural muscles [20] and dreaming [11].

After sleep onset, the sleep cycle begins with NREM sleep. After approximately 80 to 100 minutes, during which sleep progresses through deeper NREM stages, it switches to REM sleep. Afterwards, the NREM and REM phases keep changing in cyclic fashion with an approximately 90 minute long period. The duration of REM sleep episodes increases during the course of the night [11]. This sleep-cycle concept is only relevant in healthy young subjects. The structure of sleep changes in aging subjects. Sleep becomes more fragmented with age [21], sleep disturbances, such as periodic limb movement during sleep (PLMS) become more prevalent [22] and in the elderly with organic brain dysfunctions, there is a decrease in the overall amount of REM sleep [23], correlating with a decline of intellectual functioning [24].

The main part of the sleep-promoting network is thought to be the ventrolateral preoptic nucleus (VLPO) of the hypothalamus. Its role in sleep regulation was identified in 1996 [25] but already since the 1930s, it has been known that lesions in this area cause profound insomnia in humans [26]. VLPO consists of GABAergic neurons that also often contain galanin [27]. VLPO neurons are selectively firing during sleep and through their projections inhibit activity of the arousal system [28]. It is likely that other sleep-promoting neuronal networks, such as for example hypothalamic median preoptic nucleus (MnPO), participate in the induction and sustaining of sleep. Switching from NREM to REM sleep is associated with ponto-geniculo-occipital (PGO) waves, high-voltage EEG waves in pons, lateral geniculate and occipital cortex [29] (Sakai 1980). The pons in particular seems to play an important role in the promotion of REM sleep, which becomes disrupted after lesions of the dorsolateral pontomesencephalic tegmentum-cholinergic cell area [30]. Another part of the brain that is selectively active during REM sleep is the sublaterodorsal nucleus (SLD). It projects to the brainstem and spine and is possibly responsible for motoneuron hyperpolarization causing the REM-specific atonia [31].

2.3. Regulation of cycles in sleep and waking

The sleep-wake regulation is currently viewed as a two-process mechanism [32]. The two processes are called homeostatic sleep drive and circadian drive. The homeostatic sleep drive can be described simply as a consequence of an increase in a sleep-promoting substance(s), which accumulates over time following the last period of sleep. The substance is then dissipated gradually during the next sleep period as a function of the sleep periods length [33]. Even though the identity of the specific sleep factors remains unknown, evidence suggests that prolonged wakefulness is followed by NREM sleep with more intense slow EEG waves, which tend to decrease during the time spent asleep [34]. The circadian drive controls time of day when sleep is initiated via the central circadian pacemaker, the suprachiasmatical nucleus (SCN) (see Chapter 3). After waking up in the morning, the homeostatic sleep factors gradually accumulate with time starting from the last period of sleep. At the same time, the circadian drive for arousal increases and is thus able to maintain wake notwithstanding the rise in the homeostatic pressure for the sleep onset. During the late evening, the homeostatic sleep-promoting factors continue to accumulate, however, the circadian drive begins to decline and finally, in the evening, sleep onset is triggered by high homeostatic drive pressure and low circadian alerting drive. [33] (Fig.1.)

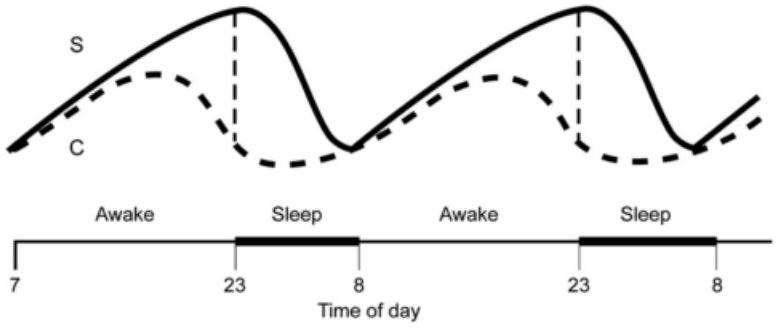

Fig.1. The two-process model of sleep-wake regulation via interaction of homeostatic and circadian sleep over 2 days [33].

3. The mammalian circadian system

Most physiological and behavioral processes in mammals follow daily oscillations. The circadian system is an internal timing system responsible for these oscillations. Circadian system receives time cues from the environment, allows organisms to entrain their circadian clock and therefore enables them to anticipate the daily changes in the day-night cycle and adapt to different photoperiods during the course of the year. Organisms are thus able to organize their physiology and behavior not just as a response to environmental processes, but are capable of proactively anticipating the changes in advance. Circadian rhythms are involved in controlling many key processes in living organisms, such as sleep and waking, glucose, lipid and drug metabolism, heart rate, release of stress and growth hormones, immunity and the cell-division cycle [35]–[41].

The main component of the circadian system in general, regardless of phylogenetic origin, is an autonomous master circadian pacemaker. The pacemaker receives light input and its output pathways regulate physiology and behavior of the whole organism [42]. Other crucial circadian system components are the oscillators located in cells of peripheral tissues. They are capable of producing rhythms on their own, but are synchronized by neural and hormonal signals from the master pacemaker [43].

3.1. The Central Pacemaker

The mammalian central pacemaker is located in the suprachiasmatical nucleus (SCN), a pair structure above the *chiasma opticum* in the hypothalamus [44], [45]. The SCN functions as a self-governing oscillator, generating rhythmic output [46]. Individual neurons of the SCN oscillate autonomously and it is their synchronized activity in vivo which enables the pacemaker to generate robust oscillations [47]. Structurally, the SCN consists of two main neuronal subpopulations, the core and the shell [48]. The term core describes the ventrolateral part of the nucleus, located close to the optical chiasm, which comprises neurons producing vasoactive intestinal peptide (VIP) and gastrin releasing peptide (GRP). The shell of the SCN is located dorsomedially and contains a population of arginine vasopressin (AVP) immunoreactive neurons [49]. The two parts of suprachiasmatic nucleus receive input and project to certain areas relative to their different functions.

3.2. Projections of the Suprachiasmatical Nucleus

The ventrolateral core obtains direct input from the photosensitive ganglion cells of the retina via the monosynaptic retino-hypothalamic tract (RHT) [45]. The RHT also projects to the intergeniculate leaflets (IGL) [50], [51]. Projections from the IGL to the SCN core, the geniculo-hypothalamic tract (GHT), provide the SCN with secondary information on retinal stimulation [50], [52]. Input into the SCN shell comes from the limbic system, hypothalamus and brainstem [53] (Moore 1996). The shell also receives input from the core, integrates it with non-visual inputs and projects to a wide set of effector areas [54].

The efferent projections of the SCN reach a variety of brain sites [55]. The efferent axons terminate in many areas of the hypothalamus, such as subparaventricular zone (sPVZ), bed nucleus of the stria terminalis (BNST), lateral septum (LS), dorsomedial hypothalamus (DMH) and the arcuate nucleus (ARC) [56]. In the thalamus, SCN projections innervate amongst others the paraventricular nucleus (PVN) [56]. Individual SCN subdivisions project to specific areas and the projection patterns can differ between species [57].

3.3. Peripheral oscillators

The peripheral oscillators consist of the same molecular components as the central clock in the SCN neurons [58] and they function in most cells of the peripheral tissue [59], [60]. Peripheral organs are responsible for many physiological functions that are subject to daily oscillations. Transcriptome studies of organs, such as liver, adrenal gland or heart, revealed that many cellular functions might be controlled by circadian regulation as well [61]–[65]. Although the peripheral oscillators seem to function in a way similar to the central clock, they are unable to synchronize their phases without the master oscillator and exhibit large phase differences in SCN-lesioned animals [43], [66]. The direct entrainment of the peripheral clock phase by the central pacemaker is achieved by humoral and neuronal signalization from the SCN [67], [68]. In many tissues, the coordination of the peripheral clocks is accomplished by processes indirectly controlled by the SCN, such as feeding rhythms (driven by rest-activity rhythms) or body temperature rhythms [59], [69], [70].

3.4. Molecular circuitry of the mammalian clock

The intracellular clock mechanism can be described as a negative-feedback loop with a delay between the stimulus and response. The negative-feedback loop controls the transcription of clock genes by different transcription factors. In mammals, the two essential transcription factors are CLOCK (Circadian Locomotor Output Cycles Kaput) and BMAL1(Brain and Muscle ARNT-Like 1) (Aryl Hydrocarbon Receptor Nuclear Translocator) [71], [72]. They contain the PAS (Period-Arnt-Singleminded) sequence allowing them to form heterodimers that activate transcription by binding to the E-box enhancers of their target genes in the morning [71], [73]. The CLOCK-BMAL1 heterodimer specifically initiates transcription of the *period* genes (*Per, Per2*) and two *cryptochrome* genes (*Cry1 and Cry2*). The produced PER and CRY proteins accumulate during the day, form heterodimers and then translocate to the nucleus, where they bind to the CLOCK/BMAL1 activation complex and inhibit transcription, thus closing the negative feedback loop in the evening [74]–[76]. The inhibition PER/CRY complex is then degraded at the end of the night for the cycle to be able to start again. The clock mechanism is stabilized by rhythmic regulation of *Bmal1* transcription. REV-ERBα inhibits *Bmal1* transcription during the day by binding to the gene promoter and the transcription is activated by RORa (RAR-related orphan receptor alpha) during the night [77], [78].

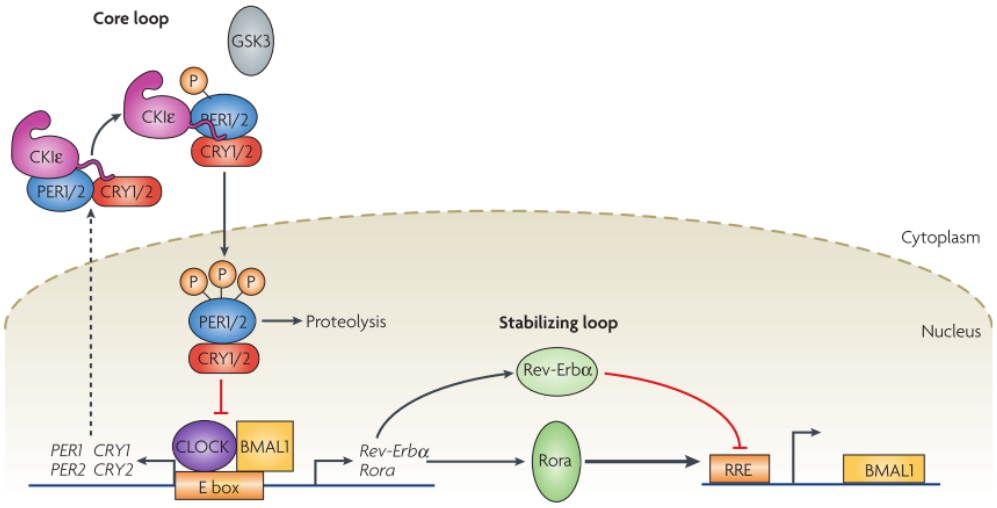

Fig.2. The molecular circuitry of the mammalian circadian cellular clock. [79]

4. Methods used for studying circadian system in humans

4.1. **In vivo m**ethods

4.1.1. Sleep, locomotor activity and body temperature

Sleep-wake cycle pattern is a well recognized output of the circadian system and can be used to assess the function of a person's circadian system. Possible methods for evaluating sleep patterns include questionnaires [80] and self-reported sleep diaries [81]. Because of their subjective nature, these methods are frequently combined with locomotor activity measuring. Circadian rhythm patterns of locomotor activity can be measured by actigraphy, a method using wrist devices collecting data on wrist movements. Some types of devices can also be used to record light exposure [82].

Sleep architecture can be evaluated by polysomnography, a method combining monitoring of brain activity by electroencephalography (EEG), eye movements by electrooculography (EOG), heart rhythm by electrocardiography (EKG), activity of muscles by electromyography (EMG) [83].

Core body temperature measurements can also provide information about the circadian clock output [84]. Compared to actigraphy, this method is less expensive, but due to significant masking factors, like sleep or food intake, it should be used in constant routine conditions.

4.1.2. Hormones

Secretion of many hormones in the human body is under the circadian control [85]. Melatonin and cortisol are hormones most frequently used as markers in studies of circadian rhythm. Melatonin has a well defined circadian pattern of secretion with low levels during the day and high levels at night. The main advantage of using melatonin as a marker is the fact that its secretion from the pineal gland is directly controlled by the central pacemaker, the SCN [86]. It also has to be taken into account that melatonin secretion is acutely suppressed by light exposure [87]

Melatonin levels can be detected directly in samples of saliva, blood, and indirectly, by detection of its metabolite 6-sulfatoxymelatonin, in urine. Techniques used for the detection are radioimmunoassay and enzyme-linked immuno sorbent assay [88], [89]. The levels of melatonin can be either measured in constant intervals over a period of 24 or more hours. The other approach is frequent sampling around the time of expected rise of melatonin level allowing to detect dim light melatonin onset (DLMO), which is often used for evaluation of the subjects' circadian phase [90].

4.1.3. Clock gene expression

The expression patterns of clock genes, or other genes controlled by the circadian clock, detected in peripheral tissue can be used to assess the functional state of the circadian system. Tissue samples can be collected in different intervals throughout the day. To collect samples, both invasive and non-invasive techniques can be used. Biopsy, which has been used in several studies [91], [92], yields high-quality samples, but is the most invasive option. Blood cells are commonly used for clock gene expression detection, however, collecting blood samples needs to be performed in a hospital [93], [94]. The non-invasive methods involve taking samples of oral mucosa [95], [96] or hair follicles [97]. These methods are suitable for experiments under real-life conditions, because patients are able to collect the samples themselves. Gene expression levels in the collected samples are determined by quantitative real-time polymerase chain reaction (qPCR).

4.2. *In vitro* methods

4.2.1. Clock gene expression

Human cells cultured *in vitro* can be used to detect expression of clock genes either by qPCR of samples collected from the cell culture at regular intervals or in real time, using tissues and cell lines from transgenic animals [60], [98]. In these animals, a reporter gene (e.g. luciferase) is inserted following the clock gene promoter, allowing real-time observation of clock gene expression as cycles in bioluminescence. Human cells used for *in vitro* assessment include adipose cells [99], islet cells [100], blood cells [101], mesenchymal stem cells [102] and fibroblasts cultivated from skin biopsies [98], [103].

5. Neuropsychiatric disorders and circadian disturbances

5.1. Neurodegenerative diseases

5.1.1. Parkinson's disease

Parkinson's disease (PD) is a progressive neurodegenerative disease affecting approximately 0,3% of the population [104]. PD symptoms include tremor, rigidity, impaired balance and bradykinesia [105]. The cause of the disease lies in the pathology of the dopaminergic system of the brain. The motor symptoms are caused by a degeneration of dopaminergic neurons in substantia nigra and striatum [106]. Non-motor symptoms, including depression or sleep-wake cycle impairment, are effected by neurodegeneration other brain areas, such as locus coeruleus and pedunculopotine nucleus [107]. Death usually occurs after 10 to 25 years following the onset of symptoms.

Sleep disruption is a very common problem in PD, affecting as much as 90% of patients [108]–[110]. The most frequent sleep disorders include insomnia and sleep fragmentation, with more wake-episodes at night and sleep bouts during the day [111] [112]. Excessive daytime sleepiness (EDS), causing the increase in diurnal sleep in patients with PD, was associated with a loss of hypothalamic orexins in a post-mortem study [113]. Disrupted sleep may possibly aggravate other PD symptoms like depression [114]. Patients' quality of life is also affected by changes in autonomic functions. Both sympathetic and parasympathetic activity decreases with the disease progression [112] and blood pressure rhythm of PD patients is changed [115]–[117]. Changes in melatonin rhythm [118] and cortisol production [119] have also been found in PD. Together with the daily fluctuations of motor activity and responsiveness to dopaminergic treatment [120] this might suggest a circadian rhythm dysfunction is involved in PD progression [121]. Furthermore, recent studies of clock genes have found Both *Bmal1* and *Bmal2* to be repressed in PD, possibly affecting the molecular machinery of the clock [122], [123].

5.1.2. Huntington's disease

Huntington's disease (HD) is a rare fatal neurodegenerative disease caused by an abnormal expansion of CAG repeats in the gene encoding the protein huntingtin [124]. The disease typically presents in the 4th decade of life and the average survival is 15-25 years from the disease onset (Bates 2002). HD can be described as a motor disorder with characteristic involuntary choreiform movements and bradykinesia, rigidity and postural

instability occurring increasingly during the disease progression [125], [126]. Non-motor symptoms include progressive cognitive impairment [127] and psychiatric disturbances [128].

Disturbances in sleep and circadian rhythms are an important part of HD and appear from the early stages of the disease [129]–[131]. With the disease progression, the overall REM sleep shortens [129] and sleep initiation and maintenance is impaired [132], resulting in reduced sleep efficiency [133], [134]. The delay in sleep onset and wake-up time in HD patients [135], together with changes in melatonin and cortisol rhythms [136], [137], suggest a phase-shift in the circadian sleep-wake cycle. A post-mortem study found a significant loss of VIP and AVP immunoreactive neurons and an mRNA/protein disbalance in the SCN of HD patients, [138]. The R6/2 mouse model of Huntington's disease also shows disturbed day-night activity profile, worsening with the disease progression [139], [140]. Interestingly, the clock gene expression which is disrupted in the mouse model in vivo [139] remains intact in vitro [141]. The circadian and sleep abnormalities of the R6/2 mouse [142] have also been linked to orexin cells in the hypothalamus, which exhibit an abnormal circadian activity profile [143].

5.1.3. Amyotrophic Lateral Sclerosis

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease with late-onset, usually after 45 years of age [144]. It affects more than 2 per 100.000 persons [145]. The disease is caused by a gradual degeneration of motor neurons in the motor cortex, brainstem and spinal cord, leading to muscle weakening, sleep disordered breathing (SDB) and finally paralysis [146]. The familial form of the disease, accounting for about 10% of cases, is caused by a dominant mutation in the gene encoding Cu/Zn superoxide dismutase (SOD1) [147].

Recent studies show that the ALS patients overall sleep is reduced, with both REM and SWS sleep shortened, resulting in EDS [148], [149]. The quality of sleep deteriorates with disease progression and patients suffering from sleep dysfunctions are more prone to depressions [149]. The circadian rhythm of cortisol production is disrupted in ALS, caused probably by dysregulation of adrenal activity [150]. Melatonin supplements were found to slow disease progression in mouse models of ALS [151].

5.2. Psychiatric disorders

5.2.1. Schizophrenia

Schizophrenia is a complex psychiatric disorder affecting approximately 1% of the population [152]. The disease onset typically occurs in late adolescence and it presents with positive and negative symptom groups. The positive symptoms include delusions, whereas the negative are represented by lack of motivation and decrease in emotional expression [153]. Cognitive processes are affected as well [154]. The disease affects several neurotransmitter systems of the brain, such as dopamine and serotonin [155].

Disruption of sleep and circadian rhythm is a well recognized feature of schizophrenia today [156]. However, the character of found circadian dysfunctions varies greatly [157], [158]. The most common in problem in schizophrenia patients are difficulties in sleep initiation and maintenance [159], [160]. The resulting sleep deprivation can exacerbate cognitive impairment in schizophrenia patients [157]. Improvement of sleep quality on the contrary, correlates with the amelioration of psychiatric symptoms [161]. Studies of clock genes have previously implicated *Clock* and *Per3* abnormalities in the pathophysiology of schizophrenia [162], [163], but larger studies failed to confirm these results [164], [165]. The mouse with SNAP-25 mutation, used as a schizophrenia model, exhibits disrupted rest-activity rhythms and phase advanced rhythm of arginine vasopressin and corticosterone, despite normal clock gene rhythm in the SCN [166]. Furthermore, the SNAP/25 protein has been linked to schizophrenia in genetic studies [167], [168].

5.2.2. Obsessive-Compulsive disorder

Obsessive-compulsive disorder (OCD) is a chronic neuropsychiatric disorder characterized by recurrent intrusive thoughts (obsessions), associated with anxiety, and by repetitive ritualistic behavioral or mental actions (compulsions), which decrease the level of anxiety [169]. OCD affects approximately 2-3% of the population [170] and results in impaired social and occupational functioning. Onset of the disease can occur in puberty or earlier [171] or following a stressful event [172].

A connection between circadian abnormalities and OCD has been proposed based on the hormonal dysregulation [173]–[175] and delayed sleep phase detected in patients suffering from the disease. Altered hormonal levels in OCD include cortisol and adrenocorticotrophic hormone (ACTH). Both of these stress hormones have unchanged profiles in OCD patients, but their secretion is significantly elevated [174], [176]. A study of children and adolescents with OCD revealed that their cortisol level decreased in response to a psychological stressor, whereas in healthy subjects the cortisol response was positive [177]. The night-time peak of melatonin secretion of OCD patients was found to be reduced and delayed by 2 hours, when compared to healthy controls [178]. Shortened total sleep duration and abnormal sleep architecture was observed in OCD [179], [180] and delayed sleep phase syndrome occurrence was significantly higher in OCD, possibly connecting the disorders [181], [182].

5.2.3. Major depressive disorder

Depressive disorder is characterized by a set of symptoms, including persistent sadness or anxious feelings, hopelessness and pessimism, loss of interest, fatigue and overeating or appetite loss. In major depressive disorder, the episodes of depression recur throughout a person's life and become disabling, preventing patients from functioning normally [183].

The connection between depression and circadian rhythms has been suggested based on several findings. The intensity of depression symptoms tends to change across the day, with a characteristic worsening of mood occurring in the morning [184]. The activity patterns of depressive patients are less structured [185] and show reduced activity during the day [186] and greater activity during sleep [187]. Sleep-wake cycle disruptions are reported by over 50% of patients suffering from depression [188]. It has been found that compared to healthy controls, depression patients have shorter latency to the first REM sleep episode, longer REM sleep and shortened SWS period [188], [189]. Some hormonal secretion patterns are also subject to change in depression. The amplitude of melatonin nighttime rise decreases [190] and cortisol is desynchronized from daily activity in patients compared to healthy controls [191]. CLOCK gene alterations have been found to predispose mood disorder development [192] and both *Timeless* [193] and *Cry1* and *Npas2* single nucleotide polymorphisms (SNPs) [194] were previously linked to depression.

5.2.4. Seasonal affective disorder

Seasonal affective disorder (SAD) symptomatology is similar to that of major depression. The depressive episodes are seasonally dependent and recur annually in the fall and winter with a spontaneous remission in spring and summer. Apart from the depression-like symptoms, SAD presents with increased appetite and carbohydrate craving, followed by weight gain [195].

Because of its seasonal character, it has been suggested that SAD is caused by the inability to adapt to the shortening of photoperiod in winter months [195]. One theory implicates a role of melatonin in the SAD development. Studies have shown a pronounced seasonal rhythm of melatonin in SAD patients, opposed to healthy controls with no seasonal melatonin alterations [196], [197]. Nonetheless, other studies failed to confirm these results [198]–[200]. The effectiveness of morning bright light therapy in SAD treatment, put forward by some studies [201], [202], is the base of the circadian phase shift theory. According to this theory, the basis of SAD is the desynchronization of the SCN circadian rhythm and sleep/wake cycle in SAD patients caused by the delayed dawn in winter months. However, some studies found the evening bright light therapy having the same antidepressant effect as the morning exposures [203], [204]. This results lead to a third theory, dividing SAD patients into two groups, namely to those suffering from a phase delay and those with a phase advance in their circadian rhythms [205], [206].

6. Selected neuropsychiatric diseases in detail

6.1. Alzheimer's disease

Alzheimer's disease (AD) is a devastating neurodegenerative disease and the most common cause of dementia. The disease onset rarely occurs before the age of fifty and is used to distinguish between the early- (onset under the age of 65) and late- (onset over the age of 65) onset Alzheimer's disease [207]. The disorder is characterized by an accumulation of amyloid-β (Aβ) protein [208] and hyperphosphorylation of τ protein [209], [210] , resulting in the formation of extracellular plaques and intracellular filaments. These can be observed in the brain post-mortem. Patients suffering from AD exhibit deficits in their behavioral and cognitive abilities which further deteriorate with the disease progression [211]–[214].

6.1.1. Circadian system in AD patients

6.1.1.1. Overt rhythms

In general, elderly people are often affected by circadian rhythm and sleep disorders. Among people over 65 years, more than 80% are affected [215], with the main abnormality being the reduction of circadian function amplitude [216]. The incidence is even higher among AD patients [217] and the rhythm disruption process is exacerbated [218], [219] leading to a fragmented sleep-wake cycle and increased frequency and duration of night-time awakenings and daytime naps [220], [221]. The disruption of sleep-wake cycles was already diagnosed in patients in mild and moderate stages of the disease [222]. This disruption can lead to cognitive impairment in both AD patients and healthy elderly subjects [223], [224]. Apart from sleep-wake cycle aberrations, behavioral disturbances have been found in AD patients as well, including agitation, restlessness, verbal outbursts, wandering and aggression. These symptoms, occurring in the late afternoon or evening, are often called sundowning and have been diagnosed in 13% to 66% of AD cases [225], [226]. The endogenous circadian rhythm of core body temperature of AD patients shows a phase delay when compared to the control group of healthy age-matched subjects [227] and measurements of AD patients skin temperature have revealed a daytime raise in the temperature of proximal skin in comparison to the healthy elderly [228].

6.1.1.2. Suprachiasmatic nuclei and AD

Post-mortem studies of patients suffering from severe AD have discovered degenerative changes in their suprachiasmatical nuclei. The AD-specific SCN neuropathologies included pretangles [229], tangles and a small number of amyloid plaques [230].

In healthy aging subjects, the overall SCN volume was found to be decreased [231], with specific damage of some neuronal populations. The AVP-expressing neurons in the SCN were found to decrease in numbers with age [232] and their circadian expression fluctuations diminish from the age of 50 onwards [233], [234]. In AD patients, this SCN AVP-expressing neuron reduction occurs even earlier and is more pronounced [232], [235]. The amount of *Avp* mRNA in the SCN was found to be three times lower in AD patients than in healthy, age- and sex-matched controls and its daily profiles were arrhythmic [236]. A recent study placed the reduction of *Avp* gene expression into the earliest stages of the disease [237]. VIP- and neurotensin-expressing neurons were also noted to be significantly reduced in AD patients [230], [238]. This loss of neuronal density in the SCN is compensated by an increase in the numbers of astrocytes [230]. The neuron/glia ratio, which determines the progression of neuropathology in SCN, correlates with the extent of circadian rhythm impairment in both body temperature and activity rhythms [239] [240].

6.1.1.3. Melatonin and AD

Levels of hormone melatonin significantly decrease in the healthy aging subjects following the circadian rhythm dampening [241]. In AD patients, this reduction is even more distinct [242]. It correlates with the AD neuropathology progression and the decrease of melatonin levels has been detected even in the cerebrospinal fluid of cognitively intact preclinical AD subjects [243]. The number of MT1 melatonin receptors in the SCN was also reduced in ageing, and in patients in the most advanced stages of AD, the number of neurons expressing the melatonin receptor was strongly diminished in comparison to the aged controls [244].

6.1.1.4. Clock genes and AD

A recent study of clock gene expression in AD patients focused on *Per1*, *Per2* and *Bmal1* genes. These genes are rhythmicaly expressed in the bed nucleus of stria terminalis (BNST), the cingulate cortex and the pineal gland of healthy subjects [245] [246]. In the brains of AD patients, PER1, PER2 and BMAL1 still exhibited well pronounced 24-hour rhythmicity, but interestingly, their oscillations in BNST, cortex and the pineal gland were desynchronized. This desynchrony is proposed to be the result of SCN cell degeneration and could be contributing to the cognitive and sleep-wake aberrations in Alzheimer's disease [247]. In another study, the rhythmic expression of *Bmal1*, *Cry1* and *Per1* in the pineal gland was examined. Whereas the genes were expressed rhythmically in healthy controls, the rhythm was completely lost in both clinical and preclinical AD patients [237].

6.1.1.5. Animal models of AD

Animal models to study AD include rats, hamsters and mice. However, none of the currently available animal models can recapitulate the disorder fully [248]. For example, many of them model only the amyloid pathology but not the τ pathology, both associated with AD.

Transgenic rats with Aβ overexpressing cells injected into their SCN showed significant deterioration of their circadian rhythms, with the rhythm waveform, period and power all being affected [249]. A similar study in hamsters revealed that after injections of Aβ into the SCN, their phase became advanced and the consistency of their diurnal rhythms decreased [250]. Both of these results were attenuated by administration of melatonin [250]. The amyloid precursor protein (APP)23 mouse model is interesting, as it shows an increase in overall dark phase activity [251] and a specific rise in the activity during the second half of the active phase [252]. The change in the activity pattern might be associated with the corresponding phenomenon of sundowning in AD patients [253]. A mouse model with both Aβ and τ pathology - the triple-transgenic (3xTg) mouse - has reduced levels of activity following the Aβ pathology onset [254] and its neuropeptidergic SCN content is changed. The number of AVP- and VIP-expressing neurons in the SCN is significantly decreased in compliance with the human post-mortem studies [254]. Another study with the 3xTg mouse has also found differences in the core body temperature rhythm, when compared to healthy controls. The temperature rhythm of 3xTg mice had greater amplitude and its phase was advanced [255].

6.2. Bipolar disorder

Bipolar disorder (BPD) is a serious mental illness, with severe mood symptoms [256]. It is characterized by a course of cyclically changing episodes of mania and depression. Bipolar disorder has been divided into two distinct types, the bipolar I disorder (BPDI), characterized by manic episodes, and bipolar II disorder (BPDII), characterized by recurrent episodes of major depression and hypomania [257]. Manic episode, the defining sign of BPDI, is marked by elevated or irritable mood, agitation, racing thoughts, impulsiveness and distractibility. The mean age of BPD onset is between 18 and 20 years of age [258]. Lifetime risk is estimated to be around 4% [259], with genetic influences accounting for as much as 60-85% of risk [260].

6.2.1. Circadian System of BPD patients

6.2.1.1. Sleep and BPD

Sleep impairment in BPD patients has been noted nearly a century ago [261] and circadian rhythm disturbances in general have been a part of bipolar disorder symptomatology for over 30 years [262]. Changes in sleep are even recognized as one of the diagnostic markers of BPD today [263]. In manic episodes of the disease, the need for sleep is reduced [263]. Sleep alterations often precede the onset of mania or depression episodes [264], thus making sleep monitoring an important part of the central relapse prevention strategy in BPD [265].

It has been suggested that REM sleep plays a role in the bipolar disorder and polysomnographic studies of BPD patients have found changes in their REM sleep architecture [266]. The latency to the first REM sleep episode was found to be shortened [267] and REM density increased [159], when compared to healthy controls. During the recurrent episodes, the sleep disruptions further worsen [268] and sleep efficiency remains impaired even in eurhythmic BPD patients, even when compared to subjects suffering from insomnia and healthy controls [269]. Importantly, the sleep disturbances experienced by BPD patients have detrimental effect on their quality of life and worsen regulation of emotions [270]. An improvement of sleep quality, on the other hand, has been found to lead to circadian rhythm stabilization [271] and is a commonly used strategy in BPD treatment [272].

6.2.1.2. Overt rhythms in BPD

Studies of a variety of parameters in BPD patients found a phase advance in their circadian rhythm. Patients in all phases of the disorder showed an advanced phase of circadian activity [273], [274]. A similar shifting of phase was also detected in the circadian rhythm of sleep, autonomic bodily functions, such as body temperature, blood pressure, pulse rate, urine volume, and humoral secretion [267], [275]–[278]. Recent study even revealed a nearly 2-hour phase advance in the rhythm of motor activity in eurhythmic BPD patients in full and sustained recovery [279].

Motor activity of BPD patients is also significantly reduced, even when compared to major depression patients [273], [280]. Concerning the humoral regulation, the spontaneous production of cortisol was found to be disinhibited in BPD patients, regardless of their medication [281]. Malfunctioning circuits of the neurotransmitters dopamine and serotonin were identified as having an important role in BPD [282], [283] and their other known functions have previously linked them to sleep [284], circadian rhythms [285] and emotions [286], suggesting a possible linking mechanism.

BPD patients also suffer from reduced heart rate variability [287] and often develop comorbid cardiovascular and pulmonary diseases, which in combination with a significantly heightened suicide risk negatively affect their longevity [288].

6.2.1.3. Circadian genes and BPD

The CLOCK gene has been previously associated with bipolar disorder [289]. A single nucleotide polymorphism of the CLOCK gene was linked to BPD symptoms, such as delayed sleep onset, reduction of sleep, insomnia and recurrence of the illness episodes [290]. *Per3* and *Bmal1* [291] and *Timeless* [163] have all been associated with BPD as well. These results were however not confirmed by larger genome-wide studies [292].

6.2.1.4. Animal models of BPD

Due to the circadian rhythm alterations in BPD, mutants of circadian genes might represent a possible strategy for modeling the disorder. Mice with an inactivated CLOCK gene are used as models exhibiting mania-like behavior. The mice are hyperactive and their cocaine reward is increased [293]. The mice also display a rise in dopaminergic activity in the ventral tegmental area (VTA) [293], a brain area implicated in reward-seeking behavior and positive affects [286]. The mania-like behavior can be successfully reversed by lithium medication [294]. Another possible BPD animal model is the forebrain-specific polymerase gamma (POLG) transgenic mouse [295]. This mouse model shows alterations of the circadian rhythm of its wheel-running activity comparable to humans suffering from insomnia and its behavioral disruptions were significantly improved by lithium treatment [296].

7. Discussion

Sleep and circadian disorders in neuropsychiatric diseases have recently started attracting more attention. The reason for this issue not being addressed earlier might be the fact that patients with neurodegenerative or psychiatric diseases generally do not complain about poor sleep quality, or other problems, indicating a circadian rhythm disturbance, and for that reason their circadian disruptions can go undiagnosed. Nowadays, the amount of evidence suggesting a role of circadian system disruption in the progression and even development of neuropsychiatric disorders is growing and many studies on this topic are being executed.

This thesis offers a summary of evidence provided up to date about the role of circadian system disruptions in neurodegenerative and psychiatric diseases. Studies of Alzheimer's and Parkinson's disease, the two most common neurodegenerative diseases, found disturbances of output rhythms of circadian system, such as disrupted sleep and hormonal rhythms. Importantly, clock gene desynchronization was also detected, suggesting an aberration of the circadian clock molecular machinery. In AD and Huntington's disease, apart from disturbed output rhythms, post-mortem studies have also identified degeneration in the SCN neuronal populations, providing evidence of direct damage to the master oscillator. In psychiatric diseases, growing evidence of circadian involvement consists mainly of a disrupted sleep pattern and changes in rhythm of hormone secretion. In addition to that, genetic studies were carried out, trying to connect BPD and depression to clock gene polymorphisms. However, the majority of genetic study results remain inconclusive.

Despite many exciting results, there are still many difficulties accompanying the acquisition of direct evidence of circadian clock state in neurodegenerative and psychiatric disorder patients. The ideal way to study circadian rhythms in neuropsychiatric disorders is to use human subjects. Here, however, researchers have to tackle several problems. The most significant one is that the master clock of the human body lies in the SCN located deep in the brain. It is therefore impossible to gain any direct data about the central pacemaker, except for post-mortem studies, which have many shortcomings, such as the lack of detailed information about lighting conditions before death. Because of this, the only way the condition of the central pacemaker can be assessed *in vivo* is by measuring its output rhythms. This can be achieved either by measuring external parameters (locomotor activity, core body temperature) or by analyzing samples of different tissues containing peripheral oscillators (secretion rhythm of melatonin or cortisol, expression of clock genes). Regardless of the tissue or

parameter studied, the studies of output rhythms can provide only indirect information on the SCN circadian clock's condition.

Another complicating factor that should not be ignored is the significant role of medication. Patients suffering from both psychiatric and neurodegenerative disorders often take medication influencing the behavior of their circadian system. For example diazepines, frequently used in treatment of various psychiatric disorders, were found to suppress nocturnal secretion of melatonin [297].

These problems could be easily overcome by the employment of animal models. However, neuropsychiatric disorders are a group of very complex diseases, usually with multifactorial etiology. Some of them are even hard to diagnose with certainty and animal model development is very complicated, so it is important to be aware that data from animal model experiments has only limited application to human patients.

Nevertheless, even though researchers have to deal with many issues and the relationship between neuropsychiatric disorders and circadian system remains unclear, the research has already led to development of some novel therapeutic approaches. Based on findings implying that circadian disorders, and sleep disturbances they cause, lead to worsening of patients‘ cognitive and psychiatric symptoms, it has been proposed that by addressing the circadian dysfunctions, it might be possible to ameliorate the patients' quality of life. This has already been successfully proven in patients suffering from BPD and schizophrenia, where the improvement of sleep quality led to an improvement in patients' well-being. Another promising fact is that bright light therapy, used for treatment of circadian rhythm disturbances, has been shown to have antidepressant effects on patients suffering from SAD and non-seasonal depression as well. Interestingly, effects of bright light have been noted even in PD, improving significantly depression, bradykinesia and rigidity in PD patients.

Research of circadian rhythms in neuropsychiatric disorders should now focus on elucidating the causal relationship between disruptions of the circadian system and the development of neuropsychiatric diseases. Furthermore, future studies should provide additional evidence using modern techniques and carefully designed experiments, and apply it to the development of treatment options, improving the quality of patients' lives.

8. Literature

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