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AGOMELATINE AS CHRONOPSYCHOPHARMACEUTICS RESTORING CIRCADIAN RHYTHMS AND ENHANCING RESILIENCE TO STRESS: A WISHFULL THINKING OR AN INNOVATIVE STRATEGY FOR SUPERIOR MANAGEMENT OF DEPRESSION?

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SUMMARY

Background: *While the research and treatment focus of biological aspects of depression has traditionally centered on neutrotransmitters disturbances, there has been relatively little attention paid to the chronobiological aspects of depression that offer rapid acting chronotherapeutis and from recently also an innovative circadian rhythms resynchronizing antidepressant.*

Objective: *This article discusses chronobiological aspects of psychiatric treatment, particularly related to depression. It is concerned with chronotherapeutics and pharmacological interventions to resychronize circadian rhythms, particularly focused on agomelatine, an innovative antidepressant targeting melatonergic M1/M2 and serotonergic 5-HT2c receptors.*

Discussion: *Depression can be explained as dysfunction at the nexus of the body, brain and mind, three mutually very dependent components, associated through circadian pace makers at the molecular, cellular, physiological and behavioral levels. Mental disorders, particularly depression, are common in people with circadian rest-activity cycle disturbances and sleep-wake problems. The circadian rest-activity and sleep-wake cycle disturbances are risk factors for developing and recurrence of mental disorders as well as, what is very important, they are associated with worse outcome. The interrelationships between circadian rhythm disturbances and depression is very complex, and the fundamental question is whether they trigger depression or whether these disturbances arise as a consequence of the disease. However, both depression and circadian rhythm disturbances may have a common aetiology: a decreased cellurar resilience associated with lower resistance to stressful events. Treating depression pharmacologicaly through the restoration of circadian rhythms may open a new era of superior management of depression and other mental disorders.*

Conclusion: *Chronotherapeutic strategies that reset the internal clock may have specific advantage for the treatment of depression and other mental disorders. There is still a lot of research to be done on utilising chronotherapeutic principles in clinical practice, particularly regarding the specific indications. Agomelatine seems to be an promising resynchronizing agent expanding the field of chronopharmacology and inducing new treatment strategy.*

Key words: *agomelatine – chronotherapeutics – chronopsychopharmacology - allostatic regulation - resilience to stress and depression*

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INTRODUCTION

It is well known that existing antidepressants are lacking in efficacy and even more in efectivenesss. Thus, we should welcome every new promising antidepressant that has a good evidence base. Agomelatine is an innovative antidepressant that works by targeting melatonergic M1/M2 and serotonergic 5-HT2C receptors. It is the first antidepressant designed to counter the disturbed biological rhythms and sleep problems associated with depressive disorders (de Bodinat et al. 2010). This is why agomelatine could be called a pharmacological chronotherapeutics or chronopsychopharmaceutics treating depression and some other mental disorders through the restoration of circadian rhythms. For time being, psychiatric chronotherapeutics have included different types of non-pharmacological manipulations of biological rhythms and sleep (light therapy, dark therapy, sleep deprivation, sleep phase delay or advance) that can rapidly improve affective disorders. Interpersonal social rhythm therapy involves learning to manage interpersonal relationships more efficiently and stabilisation of social zeitgebers, such as sleep and wake times, meal times, relax times, and timing of social contact (Frank 2005). Chronobiology and chronotherapeutics are ever gaining interest in psychiatry, pharmacy and drug delivery, particularly with regards to depressive disorders.

CHRONOBIOLOGY AND CHRONOTHERAPEUTICS IN PSYCHIATRY

Chronobiology is a field of biology that examines biological rhythms or periodic (cyclic) phenomena in living organisms and their adaptation to solar- and lunar-related rhythms, and chronopharmacology is the study of rhythmic, predictable-in-time differences in the effects/adverse events and/or pharmacokinetics of drugs, and based upon that, chronotherapeutics is the discipline concerned with the delivery of drugs according to inherent activities of a disease over a certain period of time (Jha & Bapat 2004). In addition, chronotherapeutics refers not only to medical treatment administered according to a schedule that corresponds to a patient's daily, monthly, seasonal, or yearly bio-

logical clock, in order to maximaze the health benefits and minimize adverse effects, but also to „controlled exposure to environmental stimuli and medications that act on biological (circadian) rhythms in order to achieve therapeutic effects in the treatment of psychiatric disorders“ (Benedetti et al. 2007). With regards to the main aim of psychiatric chronotherapeutics to synchronize impaired circadian rhythms, a literature review indicates three important observations: the first, mental disorders are common in people with circadian rest-activity cycle disturbances and sleep-wake problems; the second, the circadian rest-activity and sleep-wake cycle disturbances are a risk factor for developing and recurrence of mental disorders and, the third, what is very important, the circadian rhythm disorders are associated with worse outcome. In our context chronotherapeutics can be defined not only as coordinating biological rhythms with medical treatment but also as various kinds of medical treatment related to altering a patient's sleeping and waking times and resetting his or her biological clock.

It is undoubted that chronobiology may provide an effective means of adressing some of the unmeeting needs in the treatment of depression, such as shortening of the latency of onset of antidepressant action, reducing residual symptoms, enhancing resilience to stress, and preventing relapse in the long term (Wirz-Justice 2005). It is well known that the rest-activity cycles and circadian rhythm disturbances can be corrected using non-pharmacological chronotherapeutics and interpersonal social rhythm therapy (Boyce & Barriball 2010), but also administering medications like melatonin and agomelatine. Biologicaly based non-pharmacological chronotherapeutics are not only powerful adjuvant therapy, but also antidepressants in their own right (Wirz-Justice 2005). Having used the principles of chronotherapeutics from the early 1980s I have myself withnessed that these methods provide an additional improvement of treatment results (Jakovljević 1989). The effect of psychiatric non-pharmacological chronotherapeutics is claimed to be rapid but transient, and can be stabilised by its administering together with common drug treatments. The synergistic interaction between non-pharmacological chronotherapeutics and antidepressant drugs was proved in many clinical studies (Benedetti et al. 2007).

Chronotherapeutics may correct circadian rhythm abnormalities in many psychiatric disorder, but in clinical practice, there is still widespread ignorance about it. Value and importance of chronotherapeutic methods stemmed from their efficacy, rapidity of action, and lack of adverse effects. The range of chronotherapeutics' indications in psychiatry includes major depression, antepartum depression, premenstrual dysphoric disorder, jat lag and shift work disturbances, seasonal affective disorder, bipolar disorder, bulimia nervosa, ADHD and dementia, but also depression secondary to schizophrenia and Parkinson's disease (Benedetti et al. 2007). The main focus is on major depression where most of the research has been done. Beneficial antidepressant effects of various chronotherapeutic methods have been reported in all depressive conditions. With advent of agomelatine, the idea of chronopsychopharmatherapeutics or pharmacological chronotherapeutics is gaining interest in psychiatry, pharmacy and drug delivery, particularly with regards to the treatment of depressive disorders.

CHRONOBIOLOGY, SLEEP AND DEPRESSION

Synchrony between the mind-body rhythms is of the great importance for the health and normal functioning. Humans are synchronized to the rhythmic light-dark changes because their circadian pace-maker, called the suprachiasmatic nucleus (SCN), is entrained each day to the 24-hour solar cycle, which is the major „zeitgeber“ or time-giver. Other zeitgebers are food intake, work activity, or social cues. Problems with entraiment and failure to adapt to environmental and societal time cues leads to misalignment of internal biological clocks which may be followed by an increased propensity for sleep disturbances, depression, decreased immune responses, cancer, gastrointestinal, metabolic and cardiovascular disorders, etc.

Sleep restores body and mind. It is a basic human need, regulated through the interplay of homeostatic and circadian processes (see figure 1) which run independently, but in complementary fashion (Richardson 2005, Doghramji et al. 2010). The homeostatic component (process S) drives to sleep about a third of every 24-hour cycle, and the circadian component (process C) links the desire to sleep to daily fluctuations in hormones timed to the body clock. Melatonin, pineal hormone secreted in daily surges, is a synchronizer of the SCN clockwork and promotes sleepiness. Sleep is motivated behavior and people have not only a need to sleep, but also a desire for sleep as well as a fear of not being able to sleep. Then anticipated pleasure of comfortable rest facilitates sleep by inducing the state of relaxation. In state of acute or chronic distress where the pleasure response is impaired, the failure to anticipate satisfaction and to induce pleasure response contributes to the development of sleep disturbances. Sleep may occur on and off reperitively during the day, but fails to satisfy , and rarely restores any interest in getting up. Continued lack of the pleasurable anticipation of sleep in addition to anxiety and increasing anhedonia results in self-perpetuating dyssomnia. Chronic sleep insufficiency is associated with decreased cognitive performance, impaired carbohydrate tolerance, impaired acute insuline response to glucose (an early predictor of diabetes), decreased secretion of thyrotropin , alterations int he 24-hour plasma cortisol profile and compromise in immune response (see Doghramji et al. 2010).

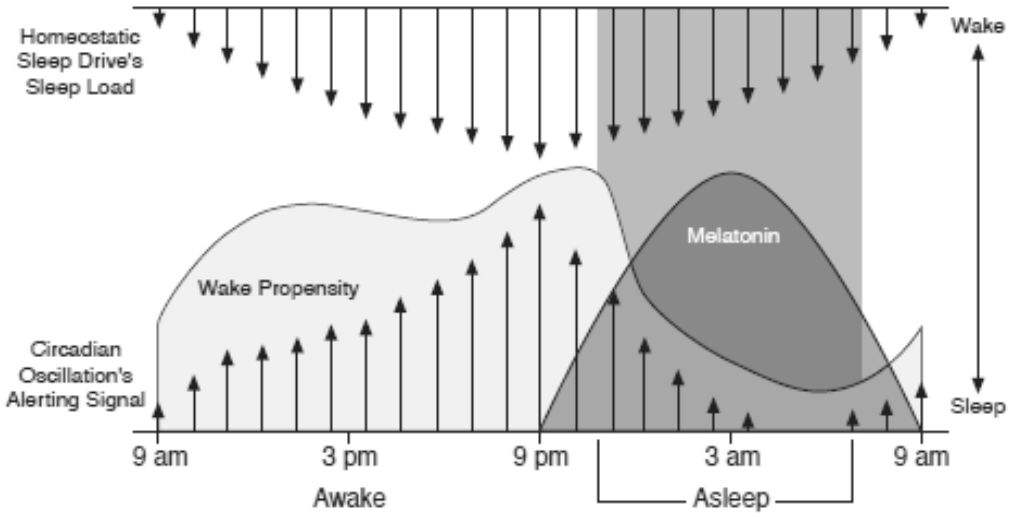

Figure 1. The two-process model of sleep regulation (from Richardson 2005, Copy right: Physicians Postgraduate Press, 2005.

Circadian rhythms are directed by a master biological clock in the SCN as well as circadian oscillators in all brain regions and peripheral tissues. Receiving information on lighting conditions directly from the retina, the SCN drives secretion of melatonin and regulates peripheral clocks, whose outputs modulate the SCN by feedback or feed-forward effects. Fasting-feeding cycles accompanying rest-activity rhythms are also important timing cues in the synchronization of many, if not most, peripheral clocks, indicating that the temporal coordination of metabolism and proliferation is a major task of the mammalian timing system (Levi & Schibler 2007). Recent studies demonstrate that circadian autonomous oscillations are also present in components of signaling cascades with a key role in neuroplasticity and cell resilience such as the mitogen activated protein kinases, brain-derived neurotrophic factor, and cAMP response element binding protein (Tardito et al. 2010). Mutation in specific SCN clock genes like CLOCK, BMAL1, and PER may be associated with motor hyperactivity, decreased sleep and mania like behavior seen in different psychiatric disorders.

Major depression is frequently associated with alterations in circadian rhythms of behaviour, sleep, core body temperature, cardiac rhythms, blood pressure, pulse, the secretion of melatonin, cortisol, growth hormone, thyrotropin and other hormones as well as inflammatory cytokines and neurotransmitters (de Bodinat et al. 2010). The most common circadian abnormality findings in patients with major depression include a blunted amplitude of daily rhythms and poor responsivenes to environmental photic and non-photic entraining stimuli (de Bodinat et al. 2010). Phase advances tend to prevail, but phase delays have also been reported, particularly in patients with seasonal affective disorder (von Zerssen 1987, Magnuson & Partonen 2005). Circadian disruption is associated to, and may in part be a consequence of, the changes in behaviour and sleep patterns that are seen in depression. Circadian desynchronization is probably triggered by an intrinsic disorganization of the SCN (de Bodinat et al. 2010, Milan 2006, Boivin 2000). The interrelationships between circadian rhythm disturbances and depression is very complex, and the fundamental question is whether they trigger depression or whether these disturbances arise as a consequence of the disease (Racagni et al. 2009). However, both depression and circadian rhythm disturbances may have a common aetiology: a decreased cellurar resilience associated with stress hypersensitivity. Treating depression pharmacologicaly through the restoration of circadian rhythms may open a new era of superior management of depression and other mental disorders.

CHRONOPHARMACOTHERAPY BASED ON THE CIRCADIAN CLOCK FUNCTION: A WISHFUL THINKING OR REALITY?

It is well known that some disease have predictable cyclic rhythms and the timing of medication regimens can improve outcome in some chronic diseases. Prevailing definition is that chronopharmacology is the discipline concerned with the variations in the pharmacological actions of various drugs over a period of time of the day, and based on this, chronotherapeutics is the disciplinary field concerned with the delivery of drugs according to inherent activities of a disease over a certain period of time (Jha & Bapta 2004). In other words, chronopharmacology studies the interaction of biologic rhythms with medications involving both the drug effects as a function of biologic timing and the drug effects upon rhythm characteristics (Reinberg 1976). The goal of chronotherapeutics is to match the

timing of treatment with the intrinsic timing of illness. Theoretically, optimum therapy is more likely to result when the right amount of drug is delivered to the correct target organ at the most appropriate time. For illustration, the correct timing of cancer treatments augments survival and diminishes the often potent side effects (Wirz-Justice 2005). Furthermore, pulsatile drug delivery is designed for chronopharmacotherapy which is based on circadian rhythm. This system by delivering a drug at right time, right place, and in right amounts, may provide benefit to the patients suffering from chronic diseases like asthma, arterial hypertension, arthritis, depression, etc.

There is a circadian rhythm in the efficacy of mental health medications, including antidepressants, mood stabilizers, antipsychotics, etc. , thus their efficacy varies depending on the time of administration (Nagayama 1999). These rhythms results from the rhythmicity in drug susceptibility in the brain, which is not related to drug pharmacokinetics, but to rhythms of neurotransmitters, receptors, and second messengers. Chronopharmacotherapy with antidepressants was tested in the 1980s and early 1990s with giving a single dose of antidepressant at three different times of day, i.e. morning, noon or before bedtime. The efficacy of clommipramine 150 mg/d given three times a day by traditional, equally divided doses, was inferior than daily single doses at noon (Nagayama et al. 1991). The absorption rate of amitryptiline 50 mg was significantly faster and higher in the morning than in the evening (Nakano & Hollister 1983). The practice of administrating single nighttime doses is justified because it reduces side effects without decreasing therapeutic efficacy.

There is growing evidence that currently used antidepressants and mood stabilizers affect the circadian rhythmicity. Lithium has been reported to lenghten the period of the circadian rhythms and to inhibit GSK-3beta, which is believed to regulate the circadian clock. Interestingly enough, valproate seems to alter the expression of several circadian genes in amygdala (see Gorwood 2010).

Agomelatine with its resynchronicing effect seems to open a new approach in chronopsychopharmaco-therapy. While it has been known for many decades that circadian and rest-activity cycles influence on the activity of antidepressants and other mental health medications, the observation that agomelatine may reset circadian clock and therapeuticaly influence on circa-dian rhythm disturbances in depression is something quite new one and very promising. From this perspective reports that clock genes mutations are involved in several diseases such as depression, metabolic syndrome, diabetes, cancer, etc. (Ohdo et al. 2010) may be of great importance for the future research and practice. Furthermore, the knowledge of intra- and inter-individual variability of molecular clock should be applied for the clinical practice in the form of pharmacotherapy based on the intra- and inter-individual variability of clock genes (Ohdo et al. 2010).

AGOMELATINE AS A POTENTIAL PHARMACOLOGICAL CHRONOTHERAPEUTICS

The relationship between circadian disruptions and depressive disorders is a topic of great interest in contemporary psychiatry. Despite the great current knowledge on neurobiological effects of antidepressant treatments, there is stil a high level of uncertainity about which all neurobiological changes are needed for full recovery from major depression. Large evidence for an involvement of the circadian clock dysfunction in depressive disorders has emerged. It seems that resinchronization or phase shifts, and stabilisation of cyrcadian rhythms are important in antidepressant treatment (Racagni et al. 2009).

Agomelatine, melatonergic MT1/MT2 receptors agonist and 5-HT2C and 5-HT2B serotonin receptors antagonist, represents an innovative antidepressant with circadian rhythms resynchronizing properties (de Bodinat et al. 2010, Fornaro et al. 2010). It needs to be taken at bed time with an initial dose of 25mg that can be increased to 50 mg if there is no satisying response within two weeks or later. Preclinical studies have demonstrated the efficacy of agomelatine to resynchronize circadian rhythm disturbances in a range of models that are representative of human pathologies in sleep (Racagni et al. 2009). Agomelatine is the most melatonin-mimic agent developed as an antidepressant drug (San et al. 2008). Agomelatine activities on circadian rhythms depends on the SCN integrity but not the pineal gland (Fornaro et al. 2010). Blockade of 5-HT2C receptors mediates excitatory neurotransmission related to release of both norepinephrine and dopamine at the frontocortical dopaminergic and adrenergic pathways (Millan et al. 2003, Milan 2009, Fornaro et al. 2010). This is why agomelatine could be also called norepinephrine and dopamine disinhibitor (NDDI) . The expression of MT1 receptors has been claimed to show diurnal rhythmicity, regulated by light and the internal clock, whereas the expressionfor mRNA of 5HT2C, but not 5-HT1A i 5-HT2A, has a circadian pattern in mammals (Lam 2006, Fornaro et al. 2010). It seems that agomelatine has a dual phased action: at night, its melatonergic sleep-promoting effects prevail over its potentially antihypnotic 5-HT2C blockade, whereas during the day its antidepressant action via 5-HT2C is uncoupled from melatonin's nocturnal action (Srinivasan et al. 2009, Fornaro et al. 2010). A GABA-ergic modulating effect in addition to 5-HT2C blockade, may explain the reported anxiolotic effects of agomelatine (Milan et al. 2005). Acute injection of agomelatine has been reported to significantly increase transcription of the brain-derived neurotrophic factor (BDNF) and activity-regulated cytoskeleton-associated

protein (ARC) in the rat frontal cortex after 16 hours (Calabrese et al. 2009). In addition to the significant role in neuroplasticity, which enables the brain to adapt to environmental stimuli, BDNF has a protective effect against glutamate toxicity, whereas both BDNF and ARC are involved in neuronal development, differentiation, and synaptic activity (Racagni et al. 2009). The last, but not the least, agomelatine showes a favorable side-effect profile, particularly concerning sexual functions, weight gain, gastrointestinal disturbances, serotonin syndrome, and treatment discontinuation syndrome.

Although the majority of studies on agomelatine have been performed on patients with major depression (Kennedy & Rizvi 2010), this circadian rhythms resynchronizing agent may show its useful or therapeutic effects in the broad range of mental disorders (Boyce & Barribal 2010). As circadian rhytms according to the desynchrozation hypothesis may play an important role in rapid cycling bipolar disorder (von Zerssen 1987), theoretically agomelatine could be selectively effective in treating depression of patients suffering of rapid cycling. What is very significant, agomelatine is not expected to have a „switching into mania“ effect frequently seen with SSRIs and other antidepressants.

CHRONOTHERAPEUTICS AGOMELATINE, RESILIENCE AND RESISTANCE TO STRESS AND DEPRESSION

In accord to vulnerability & resilience model my hypothesis here is that vulnerability for depression and susceptibility for its recurrence is associated with stress hypersensitivity and instability of circadian sinchronization system which are interconnected. The disturbances of circadian rest-activity cycles and circadian desinchronization processes may lower the cell resilience and resistance to stress, and contrary, the decreased cell resilience and low resistance to stress may induce sleep disorders and circadian disturbances. The heterogeneity of depression reflects the individual vulnerability and resilience of various interdependent neurobehavioral response systems and help us to understand why some depressed patients respond quite differently to different classes of antidepressant drugs. Acute and chronic stress may lead to sleep-wake cycles instability, insomnia and depression, but most people are resilient to such effects. Resilience refers to an individual ability to adapt successfully to acute stress, trauma or more chronic forms of adversity (Feder et al. 2009) or to a capacity to bounce back after encountering difficulties, negative events or hard times (Rutter 2006). According to some studies, resilience is related to rapid activation of the stress response and its efficient termination. Resilience is not simply the absence of maladaptive changes that occur in vulnerable individuals, rather, it is mediated by a unique set of adaptive changes. Stable and harmonized rest-activity and sleep-wake cycles are of great importance to cell resilience, allostatic regulation and resistance to stress. According to „the BDNF hypothesis“ stress reduces BDNF-mediated signalling in the hippocampus, an effect that is alleviated by chronic treatment with antidepressants (Duman & Monteggia 2006). Some evidence suggest that neurotrophic factors themselves do not control mood, but might influence networks whose physiologic functions determine how plastic changes influence mood and emotional regulation (see Amico et al. 2011). The hippocampus and prefrontal cortex, regions of great importance for higher-level cognition, play a significant role in regulating the stress respones (Dudley et al. 2011). Effects of agomelatine on the up-regulation of BDNF in the prefrontal cortex as well as on hippocampal cell survival is reported (Banasr et al. 2006, Soumier et al. 2009, Dagyte et al. 2011). It is also interesting that agomelatine may reduce the stress-induced glutamate release in prefrontal and frontal cortex (see Racagni et al. 2009).

Major depression, a notoriously heterogenous disease may be viewed as the net result of disturbances of various interdependent neurobehavioral response systems, including affective (mood) dysregulation, impaired behavioral quieting, dimished behavioral facilitation, increased stress responsivenes (Thase 1997) as well as instability of circadian sinchronization. These neurobehavioral response systems are modulated by different neurotransmitters and neurohormones: glutamate tends to have excitatory and GABA inhibitory role in these behavioral response systems, serotonin (5-HT) tends to have a permissive or tonic function, whereas norepinephrine (NE) and dopamine (DA) mainly have activating, alerting, or driving functions, while melatonin (MT), called „the hormone of darkness“, has sinchronizing and harmonizing effects. A balance between between GABA, DA and MT is proven all over the CNS (see Fornaro et al. 2010). The SCN has three major inputs of external information: the retinohypothalamic tract (RHT), the geniculo-hypothalamic tract (GHT) and nucleus raphe (NR) - (Cardinali 2010). The RHT releases glutamate and pituitary adenylate cyclase-activating polypeptide, whereas the GHT releases neuropeptide Y and GABA as neurotransmitters. Besides the RHT and GHT pathways light modulates SCN rhythmicity via the direct projections from the retina to the dorsal raphe and an abundant dorsal raphe innervation of peri-SCN neurons exists providing glutamate signaling to the SCN (Cardinali 2010). It seems that through this pathway the 5-HT2C receptors contributes to the regulation of circadian rhythmicity (Cardinali 2010). The vulnerability to stress and an individual capacity for resilience are associated with sleep-wake cycles stability and melatonergic system. In addition to its main function to trigger the mind-body nightly cycle of rest and repair, melatonin also buffers the effects of distress, boosts immune system, lowers cholesterol and blood pressure, and shows antioxidant properties (Reiter & Robinson 1995).

The autonomous circadian clocks are discovered in neurons located in many regions throughout the brain, including kye regions involved in sleep-wake regulation, mood and cognition, emotional regulation and memory formation (see Summa & Turek 2010). In addition to this fact, it is quite possible that circadian dysfunction at the cellular level may lead to decreased cellular resilience associated to altered neuronal network activity and neurotramsmitters disbalance resulting in depression. The opposite is also possible that decreased cellular resilience leads to circadian dysfunction and depression. It is also very interesting that a significant portion of transcriptome in many different tissues and organs, is under the control of the circadian clock, so that circadian disruptions are expected to exert widespread effects on transcription of key genes within the brain as well as in most peripheral organs (Summa & Turek 2010). That is why disruptions of cell-autonomous rhythms associated with decreased cell resilience may contribute to localized areas of decreased functional ability in the CNS causing subtle global deficit that underlie the depressive pathology. With regards the high-degree of control over internal synchrony within the organism by the SCN, disruptions in the normal phase relationships between rhythms in various brain regions, or between the CNS and peripheral tissues, may lead to detrimental functioning of the system, decreased stress resilience and depression. Some recent studies indicate that deltaFosB, a transcription factor inside neurons which turn multiple genes on and off, trigerring the production of proteins that perform a cell's activities, mediates resilience in the nucleus accumbens, hub of the brain's reward system. DeltaFosB is significantly depleted in brains of patients with depression while some antidepressant boost it. Induction of deltaFosB helps adaptation and coping with stress (Vialou et al. 2010). It would be interesting to investigate a possible effect of agomelatine on DeltaFosB as well as on DNA methylation. Behavioral adaptation to environmental stress was recently reported to be associated with alterations in DNA methylation that could distinguish between „PTSD-like“ and „non-PTSD-like“ responses within population (see Dudley et al. 2011). It seems that epigenetic differences in various regions of the brain are associated with a range of psychiatric disorders, including many that are stress-related (Dudley et al. 2011).

Understaning the chronobiological mechanisms of cell resilience and resistance to stress offers a crucial new dimension for the development of fundamentally novel antidepressants. Major depression is a heterogenous, long-term and incapacitating disorder, with too many patients experiencing recurrent depresive episodes or persistent residual symptoms. Different interdependent biological processes including neuroplasticity, circadian rhythms, endocrine and immune system functions have beem examined with the aim to identify subgroups of patients based on the susceptibility for depression, the risk for a recurrence, and the treatment response (Manji & Duman 2001, Antonijević 2006). Distress, alostatic load dysregulation, sleep disruption and loss are important triggers for episodes of both mania and depression, and plays an important role in the patogenesis of affective disorders. Agomelatine responds to the temporal aspects of depression in its approach to the pathophysiology of disease through the restoration of circadian rhythms, and providing clinical efficacy at all time phases of depression treatment (Munoz 2010). Resynchronizing circadian rhythms and so normalizing biological alostasis seems to provide acute and sustain symptom releif, and prevent relapse over the long term (Munoz 2010).

CONCLUSION

It is undoubtedly the combination of genes and environment, mediated by epigenetic changes at critical period of development, which confer chronobiological stability of sleep-wake cycles, cellular resilience and resistance to stress related disorders like depression. Several possible relationships may exist between depression, circadian disturbances, cellular resilience and stress resistance. The first one is that depression and circadian disturbances are concequences of decresased cellular resilience and lower resistance to stress. The second posibility includes the opposite: decreased cellular/stress resilience and depression are consequences of circadian disturbances. The third possibility is that decreased cellular/stress resilience and circadian disturbances produce reciprocal causal effects leading to depression. Agomelatine opens an innovative chronobiological approach to understanding and treating depression related to cell resilience and stress resistence model. However, we are still at the beginning of utilising chronotherapeutic principles in clinical practice and there is still a lot of research to be done particularly regarding the specific indications.

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