

Clinical Advances of Recent Discoveries about the Interaction between Circadian and Serotonergic Systems

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ABSTRACT: *The circadian rhythm and the serotonergic system have anatomical connections and convergent functional association influencing the functioning of the central nervous system. Serotonin is present in several areas of the brain that regulate the circadian rhythm and deregulations in the levels of dopamine have been associated with neurological disorders such as autism, depression, and anxiety. New discoveries have been made about the association of serotonin and circadian rhythm. Thus, the objective of the study was to address the clinical advances on the interaction of these two systems. For this, a bibliographic review in databases Scielo, PubMed, Lilacs and Cochrane was carried out, in which 40 full articles were used. Through genetic, physiological and clinical evidence, the 5-HT and circadian systems of the brain are connected to each other and converge to regulate affective behaviors and pathologies. Rates ever-increasing related to use of selective inhibitors of serotonin reuptake and other drug classes of serotonergic influences are observed, as well as an increasing prevalence of circadian disorders, especially linked to sleep problems.*

Keywords: *Serotonin, circadian rhythm, sleep, depression*

INTRODUCTION

The serotonin brain circuits 5-hydroxytryptamine (5-HT) and of the circadian rhythm constitutes two of major regulatory networks that exert widespread influence on the functioning of the central nervous system. These brain networks present, each consisting of a localized neuronal population and with a highly ordered molecular signaling, reciprocal anatomical connections, and convergent functional association. In the brain, 5-HT originates in the medial and dorsal raphe nuclei, with widespread projections throughout the brain, including for the circadian control center, the suprachiasmatic nucleus (SCN). The serotonergic system is composed of specific neurons secreting of 5-HT, with a network of genes that encode regulatory proteins, specific receptors transporters, and degrading enzymes. Deregulations of these networks have been associated with neurological disorders such as autism, depression, and anxiety (Zeitzer, 2013, Ciarleglio et al. 2011). The circadian rhythm, in turn, controls the fluctuations of our physiological and behavioral activities within the period of 24 hours, which is extremely adjusted by self-regulated expression of the called *CLOCK* genes. Circadian rhythmicity is essential for the control of energy metabolism, cycle-wake, hormone production and cognitive performance (Versteeg, Serlie, Kalsbeek, & Fleur, 2015; Wang, et al. 2016; Zouabi et al. 2016). The circadian rhythm is regulated by various brain regions, particularly mediated through 5-HT, which can be evidenced by the large number of 5-HT receptors such as the types 1A, 1B, 2A, 2C, 5A and 7 subtypes in SCN (Smith et al. 2015). Therefore, in different animal models, healthy volunteers and in patients with circadian dysfunctions, it is remarkable the importance of serotonergic neuromodulation in the maintenance of endogenous rhythms, and also in understanding how circadian dysfunction can influence the efficacy and function of the serotonergic neurotransmission (Matsumura et al. 2015; Holst, Valomon, & Landolt, 2016).

Although the circadian rhythm has the ability to function autonomously, it is constantly adapting to our environment using external cues, called zeitgebers, the main one being the light (Wang, et al. 2016). In this context, 5-HT is an important regulator of circadian rhythm, by modulating responses to photic and non-photoc zeitgebers (Smith et al. 2015; Versteeg, Serlie, Kalsbeek, & Fleur, 2015). As with the serotonergic system of the brain, deregulation of the circadian system is associated with a range of disturbance of behavior and development, including depression, bipolar disorder, autism and disorders of the sleep-wake cycle (Ciarleglio et al. 2011; Cho et al. 2016; Schaufler et al. 2016). The non-photoc serotonergic inputs in the SNC, for example, have activity influenced by nutrient intake, such a way, these inputs can stimulate the SCN in inappropriate times of the day due to poor eating habits, as overeating at night, which favors the development of the metabolic syndrome (Versteeg, Serlie, Kalsbeek, & Fleur, 2015). Nevertheless, the levels of 5-HT also exhibit circadian rhythmicity in several brain regions, including SCN, Pineal gland, raphe nuclei and corpus striatum (Barassin et al. 2002; Versteeg, Serlie, Kalsbeek, & Fleur, 2015). In experiments on mice, the disturbance of the circadian rhythm led to decrease in 5-HT expression in cell bodies (the dorsal and medial raphe nuclei) and projection areas (frontal cortex, caudate putamen, preoptic area and SCN), demonstrating a clear synergism between systems, which can contribute to the understanding of disorders (Matsumura et al. 2015).

Both serotonergic system and circadian are extensively studied in their neuroanatomical and genetic levels. Genetic variations in circadian rhythm genes are significantly associated with a large variety of neuropsychiatric disorders, such as Major Depressive Disorder (MDD) (Levebratt et al. 2010; Hua et al. 2014), winter depression (Partonem et al. 2007), dysthymia (Kovanen et al. 2013), anxiety (Sipila et al. 2010) and schizophrenia (Mansour et al. 2009). Polymorphisms associated with important genes of serotonergic transmission are also constantly associated with predisposing factors for such condition (Petito et al. 2016; Wang et al. 2016). Interestingly, the key molecules signaling of the network

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of serotonergic transmission, as the transporter gene and receptors are expressed in the SCN. In turn, the *CLOCK* gene network is also expressed in the serotonergic neurons of the raphe, regulating the key genes activity of the serotonergic transmission (Abe et al. 2002; Malek, Sage, Pévet, & Raison, 2007). In this sense, genetic alterations in the network of 5-HT genes have demonstrated a significant influence on the circadian behavior (Ciarleglio et al. 2011). Mice with deletion in the 5-HT1B receptor gene, which is located on the presynaptic terminals of retinal ganglion cells that project to the SCN, exhibit a pattern of reduction of adaptability of endogenous rhythms promoted by light (Sollars, Ogilvie, Simpson, & Pickard, 2006). Such data cooperate the discovery that agonist of this receptor can promote deviations in the important role of light in the circadian regulation (Pickard & Rea, 1997). It was also reported the association of genotypes of the 5-HT2A receptor gene with the risk of poor sleep quality after occupational stress, pointing susceptibility such genetic variations to circadian dysfunction in specific conditions (Jiang et al. 2016). Moreover, Qin et al. (2014), in a meta-analysis, demonstrated that polymorphisms of serotonin receptor (5-HTR-1438 "A") and transporter (5-HTTVNTR 10 repetitions) were significantly associated with obstructive sleep apnea syndrome (OSAS), while allele "S" of 5-HTTLPR conferred protection against the condition. Studies also suggest that men and women differ in serotonergic mediation of the hypothalamic-pituitary-adrenal axis activity, which helps to understand gender differences in predisposition to pathologies (Wankerl et al. 2010). These data, along with the development of epigenetic research, provides a strong foundation for personalized treatments, due to the influence of polymorphisms in circadian disfuncões and therapeutic sensitivity (Holst, Valomon, & Landolt, 2016).

The most commonly prescribed drugs in the pharmacotherapy of mood and anxiety disorders exert their effects through modulation of monoaminergic neurotransmission. Specifically, selective serotonin reuptake inhibitors (SSRIs), as fluoxetine, target the serotonergic system by blocking the reuptake of serotonin from the synaptic cleft through their inhibitory effect on the serotonin transporter, hence augmenting the amount of free serotonin available (Schaufler et al. 2016). Notably, due to the connection of anatomical and molecular levels, psychotropic drugs which act on neurotransmitters system such as the 5-HT, have been reported to interaction with the circadian rhythm, owing of functional and molecular alterations in the SCN (Peveler & Kendrick, 2005). Among the effects of SSRIs is the displacement of neural firing in the SCN of rats (Sprouse, Braselton, & Reynolds, 2006) and change in *CLOCK* gene expression in corpus striatum and hippocampus of mice (Uz et al. 2005). Furthermore, it has been described that fluoxetine treatment contributes to normalizing the dysfunction of locomotor rhythm and *CLOCK* gene expression in a genetic mice model of high trait anxiety and depression (Schaufler et al. 2016). Being remarkable the role of endogenous rhythms of the pathophysiology of depression (Barnard & Nolan, 2008; Monteleone & Maj, 2008). MDD and other disorders promoted by chronobiological disorders are theoretically treatable through manipulation of the circadian system using chronobiotic drugs and chronotherapy. However, for MDD, melatonin alone, the major hormone regulating chronobiological, has not antidepressant action (Salva et al. 2011).

Antidepressants with chronobiological intrinsic properties offer a new approach for the treatment of depression (Salva et al. 2011). In this context, agomelatine is an agonist of melatonin receptors MT1 and MT2 in the SCN, as well as an antagonist of 5-HT receptor (2C). The antidepressant activity of the agomelatine is proposed result from the synergy between these sets of receptors, which are essential components of the circadian timing system, showing antidepressant activity in various animal models of depression and clinical studies. The drug also was indicated in the improvement of the sleep-wake cycle disorders in patients (Popoli, 2009; Kasper &

Hamon, 2009; Gahr, 2014; De Berardis et al. 2015). Considering the study of pharmacological and genetic models that address the relationship of serotonergic transmission with biological rhythms and how it implies new treatments for various disorders, cannot rule out the pharmacogenetic importance of such findings. A *CLOCK* gene polymorphism (rs3736544) for example, exhibited a significant association with therapeutic response and remission to fluvoxamine in patients with major depression. These data support the importance of the internal *CLOCK* gene on the serotonergic manipulation in the treatment of depression (Kishi et al. 2009). As demonstrated by genetic, physiological and clinical evidence, the 5-HT and circadian system of the brain are connected to each other and converge to regulate affective behavior and pathologies (Ciarleglio, Resuehr, & McMahon, 2011). The study of the association between these two important systems becomes even more important when observed ever-increasing rates of use of SSRIs and other drugs classes of serotonergic influence by population (Matsumura et al. 2015), in addition to the increasing prevalence of circadian disorders, especially linked to sleep problems (Gooley, 2016).

Conflict of Interest Statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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