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Review

Some implications of melatonin use in chronopharmacology of insomnia

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ABSTRACT

The last decade has witnessed the emergence of new chronopharmacological perspectives. In the case of sleep disorders, the accumulating evidence suggests that even a minor dysfunction in the biological clock can impact broadly upon body physiology causing increases in sleep onset latency, phase delays or advances in sleep initiation, frequent nocturnal awakenings, reduced sleep efficiency, delayed and shortened rapid eye movement sleep and increased periodic leg movements, among others. Thus, restoration of the adequate circadian pattern of proper sleep hygiene, targeted exposure to light and the use of chronobiotic drugs, such as melatonin, which affect the output phase of clock-controlled circadian rhythms, can help to recover the sleep–wake cycle. The optimization of drug effects and/or minimization of toxicity by timing medications with regard to biological rhythms is known as chronotherapeutics. While chronotherapeutical approaches have been particularly successful in the treatment of hypertension, allergies and some forms of cancer, a time-dependent pharmacological approach can be also effective when dealing with sleep disruptions like insomnia. A large proportion of patients under benzodiazepine (BZD)/Z drug treatment fail to achieve a complete and sustained recovery and are left with residual symptoms, like tolerance or dependency, that make relapse or recurrence more likely, and poorer quality of life a reality. Thus the chronic and extensive use of BZD/Z drugs has become a public health issue and has led to multiple campaigns to reduce both prescription and consumption of BZD/Z-drugs. This short review discusses available data on the efficacy of melatonin to reduce chronic BZD use in insomnia patients.

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1. Introduction

While the study of circadian rhythms has flourished in recent decades, including the discovery of the mammalian master biological clock in the hypothalamic suprachiasmatic nuclei (SCN) (Moore, 2013; Welsh et al., 2010), its core molecular machinery (Buhr and Takahashi, 2013; Ko and Takahashi, 2006; Partch et al., 2014) and its entrainment mechanisms (Golombek and Rosenstein, 2010), the application of chronobiological principles to clinical medicine and, more specifically, therapeutics, has not followed at the same pace. As an integrative discipline in physiology and medical research, chronobiology renders possible the discovery of new therapeutic tools addressing central mechanisms in various diseases. Indeed, recent research has paved the path for specific chronobiological applications for the clinical practice in diverse fields, including neurology (Bruni et al., 2015), psychiatry (Baron and Reid, 2014), cardiac and respiratory disease (Smolensky et al., 2015a) and clinical oncology (Innominato et al., 2014). Moreover, there is an increasing understanding of the role of the biological timing system in metabolic processes, with the implications that disrupted sleep and/or circadian rhythms can lead to severe metabolic disturbances (Depner et al., 2014; Summa and Turek, 2014).

In the case of human sleep, its duration and organization critically depend on its circadian phase (Czeisler et al., 1980) and is regulated by the interplay of homeostatic and circadian processes which run independently, but in complementary fashion. 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 (Achermann and Borbely, 2003). Melatonin, a pineal hormone secreted in daily surges, is a synchronizer of the SCN clockwork and promotes sleepiness (Cardinali et al., 2012a).

The general health detrimental effect of disrupted sleep has long been established empirically. Epidemiological studies have shown that disturbed sleep-comprising short, low-quality, and mistimed sleep-increases the risk of metabolic diseases, especially obesity and type 2 diabetes mellitus (Cedernaes et al., 2015) as well as in neurodegenerative disorders (Landry and Liu-Ambrose, 2014). In cancer sleep disorders are very common (Howell et al., 2014) but they generally remained underdiagnosed and poorly treated (Dahiya et al., 2013).

Insomnia is a condition of unsatisfactory sleep, either in terms of sleep onset, sleep maintenance, early morning awakening or feeling unrefreshed. It is also a disorder that affects daytime and subjective well-being, skills and performance. Akin to pain disorder, insomnia is a subjective disorder amenable of diagnosis through clinical observations rather than through objective measurements. Epidemiological surveys indicate that up to 40% of individuals over 65 years of age are dissatisfied with their sleep or report trouble in initiating and maintaining sleep, and that 12–25% complain of persistent insomnia (Neikrug and Ancoli-Israel, 2010; Wolkove et al., 2007a,b). Hence up to 30–40% of seniors use sedative hypnotic benzodiazepines (BZD) and related medication (type Z drugs). This is a cause for concern due to undesirable side effects, e.g. dependency. It is also known that the older population responds to drugs differently and less predictably than their younger counterparts (Boyle et al., 2010; Faught, 2007). Since there is consensus in that therapies for treating disruptions to sleep must be focused on normalizing the underlying cause of these disruptions (Smolensky et al., 2015b), a breakthrough in chronopharmaceutical formulation against insomnia would be one that addresses the oscillatory nature of the human sleeping process. The main purpose of this review article is to offer an update of chronopharmacological concepts, implications and applications, with a specific emphasis on the use of the pineal hormone melatonin for the treatment of sleep disorders.

2. Some basic concepts on chronopharmacology

Chronopharmacology was recognized in the early days of biological rhythm research as one obvious application of chronobiology, which takes into account the variations of drug effects depending on the timing of administration (Halberg, 1969). Chronopharmacology involves both the investigation of drug effects as a function of biological timing mechanisms and the investigation of drug effects upon body rhythms. In terms of drug effects, temporal variations might affect their pharmacokinetics (i.e., chronokinetics) because of underlying changes in absorption, distribution, metabolism and general bioavailability (Bruguerolle et al., 2008), or its pharmacodynamics, reflected by changes in the expression of drug receptors or signal transduction mechanisms. In terms of psychotropic drugs, chronodynamics is attributed to a rhythmic neurotransmission system, such as temporal changes in neurotransmitters, receptors, and second messengers. In the case of BZD, they have been shown to phase shift the circadian clock in a nonphotic pattern, probably by acting on γ-aminobutyric acid (GABA) receptors in the SCN (Mrosovsky and Biello, 1994; Turek and Losee-Olson, 1987; Van and Turek, 1989). In addition, time-related variations in toxicity and undesired side effects must also be taken into account (chronotoxicity) (Beauchamp and Labrecque, 2007; Erkekoglu and Baydar, 2012). Indeed, the general idea of "chronotherapeutics" has been defined as the optimization of drug effects and/or minimization of toxicity by timing medications with regard to biological rhythms (Lemmer and Labrecque, 1987). All these concepts converge into the definition of chronopharmaceutics, which deals with the design and evaluation of drug-delivery systems that release a bioactive agent with a rhythm that ideally matches the biological requirement of a given disease therapy (Lemmer, 1996, 2005; Youan, 2004). Chronotherapy advocates for the use of temporal characteristics of the patient and of the disease process to optimize the therapeutic response and minimize the undesirable side effects of a drug, e.g. treatment of sleep and psychiatric disorders with either light therapy or hormonal intervention (Kaur et al., 2013; Ohdo et al., 2011a).

While an increasing number of drugs have been demonstrated to vary their effects according to the time of administration (Baraldo, 2008; Ritschel and Forusz, 1994), the application of such concepts remains elusive. The main examples of chronopharmacological treatment refer to drugs affecting blood pressure (Hermida et al., 2013; Portaluppi et al., 2012; Schillaci et al., 2015; Stranges et al., 2015), kidney disease, respiratory disease (Byers and Noll, 1995; Martin, 1993; Smolensky et al., 1999; Smolensky et al., 2007) and cancer (Levi et al., 2010; Ohdo et al., 2011b; Ortiz-Tudela et al., 2013; Sewlall et al., 2010). Since the time-related effect of drugs depends on the activity of circadian clocks, we will give a brief overview of such pacemakers' activity before focusing on chronopharmacological implications on sleep management.

3. Biological rhythms: an overview

Circadian rhythms are driven by endogenous pacemakers that have periods that, in the absence of external time cues, are approximately 24 h in length. In the presence of time cues, generally with a period equal to that of the solar day, the clock and the rhythms it drives are adjusted to an exact 24-h period (Golombek and Rosenstein, 2010). The external rhythms that achieve this entrainment of the endogenous oscillator are termed zeitgebers. In humans, the most important is the light/dark cycle, perceived by