The Physiological and Psychological Effects of the Relationship Between Cryptochromes and Circadian Rhythm on Mammals and Plants

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***Abstract*—The circadian rhythm is extremely important for the health of living organisms. Disruption of the circadian rhythm has many adverse effects on living organisms. This review discusses the connection between cryptochromes and the circadian rhythm and the physiological effects of this connection on plants and mammals. In addition, in the final section, This review discusses mood disorders observed in humans associated with circadian rhythm. It has been observed that cryptochromes are particularly involved in activities related to the day-night cycle and, consequently, regulate various metabolic activities.**

I. INTRODUCTION

Crys (Cryptochromes) are found in many kingdoms, from bacteria to mammals. This enables many light-dependent physiological events to occur in living organisms. For example, Crys proteins repair DNA damage caused by ultraviolet radiation through a mechanism known as photoreactivation. In addition, they can regulate circadian rhythms (*circa*= about, *dies*=day), flowering times, and light morphogenesis in plants across all major evolutionary kingdoms.

In mammals, Crys play a role in regulating behavioural rhythms. They are also involved in controlling sleep, which is extremely important for our mental health. For example, they play an indirect role in the emergence of diseases such as several types of cancer, elevated incidence of cardiovascular and metabolic disorders, as well as increased prevalence of behavioural health and psychiatric disorders, which can be seen in relation to sleep. [1]

II. METHODOLOGY

The fundamental question in this study was 'What are the consequences of the relationship between circadian rhythms and cryptochromes?' Based on this question, studies in the literature concerning their effects in plants and mammals were identified. Subsequently, the information in the literature was compiled and this article was written in an accessible language.

III. RELATIONSHIP BETWEEN CRYPTOCHROMES AND CIRCADIAN RYTHM

It should first be noted that the circadian rhythm is not solely dependent on the sleep-wake cycle. The circadian rhythm is dependent on environmental factors known as 'zeitgebers'. However, light is the most important zeitgeber for the circadian rhythm. In fact, it is the most important zeitgeber for the Suprachiasmatic Nucleus located in the hypothalamus region of mammals. [8]

The circadian rhythm, which enables organisms to respond to changing conditions throughout the day and prepare in advance, has provided them with an evolutionary advantage. In plants, it controls important mechanisms such as flowering time and seed dispersal time. In mammals, it is crucial for regulating metabolism. Crys collaborate with numerous genes and proteins to regulate the circadian rhythm. These aspects will be discussed in detail.

A. Cryptochromes and the effect of circadian rhythm on plants

Important differences exist between systematic, and non-systematic reviews which especially arise from methodologies used in the description of the literature sources. A non-systematic review means use of articles collected for years with the recommendations of your colleagues, while systematic review is based on struggles to search for and find the best possible research which will respond to the questions predetermined at the start of the review.

In plants, the clock core that generates the 24-h rhythm includes a highly complex network of genes that act as repressors and/or activators, creating multiple interlocked transcriptional feedback loops formed by transcription factors.

Clock genes exhibit temporal expression waves that reach high activity at different times of the day. They regulate each other's transcription by modulating many fundamental physiological processes such as flowering time, phytohormone synthesis, growth control, metabolic activities, and biotic and abiotic stress responses. MYB-like transcription factors CIRCADIAN CLOCK ASSOCIATED 1 (CCA1) and LATE ELONGATED HYPOCOTYL (LHY) reach their expression peak around dawn; They suppress the transcription of PSEUDORESPONSE REGULATOR (PRR) genes (also known as 9,7,5 and 1, Timing of CAB expression 1 (TOC1)), which are expressed in the afternoon. When TOC1 reaches its highest level in the evening, it suppresses the expression of CCA1/LHY, ensuring the cycle continues. It also affects certain genes referred to as the 'evening complex,' such as ELF3 (EARLY FLOWERING3), ELF4 (EARLY FLOWERING 4), and LUX (LUX ARRHYTHMO). These three genes show maximum transcription at night; at this time of day, they suppress several morning and afternoon genes, leading to further feedback loops. MYB-like factors such as the REVEILLE family (4,6,8) support the transcription of PRR genes and the evening complex; in particular, the complex formed by RVE8 with LNK1 and LNK2 increases the transcription of PRR5 and TOC1 in the afternoon. Thus, the PRR genes repress CCA1/LHY again, and the rhythm continues until morning. In another part of the cycle, TOC1 promotes the degradation of the ZTL protein throughout the night, while during the day, the GIGANTEA protein stabilises ZTL, blocking this interaction. [3,4]

Circadian genes regulate each other in this manner to create a rhythmic wave of expression at different times of the day, while light receptors play an important role in synchronising these cycles with external signals. Cryptochromes trigger the reduction of the chromophore to its 'signal state' by initiating an electron transfer reaction involving blue light photoactivation, conserved tryptophan residues and/or cellular metabolites. This controls the general light development programme in plants. In a second mechanism, light-activated cry2 interacts with transcription factors CRY2 INTERACTING bHLH (CIB1, 2, 4, 5) and directly activates FLOWERING LOCUS T (FT) transcription to promote flowering. This provides specialised control over the timing of flowering. [3,4]

B. Physiological effects of cryptochromes and circadian rhythms in mammals

The circadian rhythm regulates numerous mechanisms in mammals. The mechanisms controlled by the circadian rhythm have physiological and behavioural effects on mammals. For example, the SCN (suprachiasmatic nucleus) located in the hypothalamus region of mammals is responsible for the secretion of many hormones. For example, the SCN plays an important role in the expression of sex steroids (This topic will be addressed subsequently). This allows for the control of mechanisms that affect the continuity of the species, such as fertility in mammals. In addition, circadian rhythms affect the metabolism of living organisms, and their disruption can cause various physiological diseases and mood disorders (This topic will be addressed subsequently too).[1,4,8,14]

At the molecular level, the cell-autonomous molecular clock is controlled by two intertwined transcriptional/ translational positive and negative feedback loops (TTFL) in mammals. CLOCK (Circadian Locomotor Output Cycles Kaput) and BMAL1 (for brain and muscle aryl hydrocarbon receptor nuclear translocator (ARNT)like protein 1) are transcription factors that bind E-box (CACGTG) to initiate the transcription of clock-controlled genes including the *Periods* and *Cryptochromes.*[8]

The PER and CRY proteins produced from these genes then enter the cell nucleus and suppress the activity of CLOCK and BMAL1, thereby shutting down the system. In a second control loop, retinoid-related orphan receptors (ROR a,b,g) proteins initiate the transcriptional activation of Bmal1, while REV-ERBs suppress these activities. This dual effect allows the biological clock to be finely tuned. Furthermore, the constant chemical modifications these proteins undergo within the cell, such as phosphorylation, ubiquitination, sumoylation, and acetylation, are essential for the rhythm to function regularly. In particular, PER:CRY ubiquitin-dependent degradation contributes to the precise regulation of the molecular clock. [8]

It must be emphasized that one of the most important factors in regulating the circadian rhythm in mammals is the sleep-wake cycle. I have previously mentioned that many diseases and biological irregularities can arise in relation to the sleep-wake cycle. Fertility is the first topic addressed.

Menstrual irregularities, dysmenorrhea, increased time to, and reduced rates for, conception, increased miscarriages, lower birth weights are among the adverse reproductive health outcomes that have been linked to circadian rhythm disorders in studies. At this point, the factor that most disrupts the circadian rhythm is sleep. To examine the effects of the circadian rhythm on fertility, the mechanism by which sleep disrupts this rhythm must be considered. [14].

There are at least three possible ways in which sleep disorders may be associated with infertility: 1) HPA axis activation, which triggers sleep disorders, may also affect reproduction. Changes in sleep duration and/or sleep continuity disorders may themselves impair reproduction or lead to further increases in HPA axis activation; 3) HPA axis activation may cause infertility independently of (or in interaction with) sleep duration and/or sleep continuity disorder. The effect of sleep on fertility in women is extensive and detailed. This article summarizes this topic. (For more information, see reference [14])

However, there is one point I would like to highlight in this regard: melatonin. Evidence has been presented regarding the beneficial effects of melatonin on reproductive functions in animals and humans. Melatonin is thought to have significant effects, particularly in seasonally breeding mammals, facilitating oocyte quality and development, ovulation, luteal function, and embryo development. Findings have been made regarding the antioxidant effects of melatonin and its ability to increase fertility. Melatonin is highlighted here due to its effect on it has an effect on many reproductive hormones. Fertility in women is not solely dependent on the melatonin hormone. There are many hormones regulated by sleep. For example, hormones such as Thyroid Stimulating Hormone (TSH), Luteinising Hormone (LH), Follicle Stimulating Hormone (FSH), Prolactin (PRL), Testosterone, Oestradiol, Anti-Mullerian Hormone (AMH), and Progesterone have effects on reproductive mechanisms in women. [14] However, the details of these are not provided in this article.

The effect of circadian rhythm on fertility in males is similar to that in females. A decrease in sperm quality and count has been observed in males with poor sleep duration and quality. The main reason for this is hormonal changes related to sleep. Testosterone levels are highest during the day and lowest in the evening. There is evidence that sleeping less than 6 hours at night reduces sperm concentration. It has been observed that lack of sleep reduces testosterone release but increases corticosterone and cortisol levels. This mechanism has not been fully elucidated. However, it is thought that sleep deprivation activates the hypothalamic-pituitary-adrenal (HPA) axis, increasing cortisol and corticosterone levels, and that this feedback inhibits the hypothalamic-pituitary-gonadal (HPG) axis, reducing testosterone secretion. Due to the extensive nature of this topic, the effect of circadian rhythm on fertility in women is summarized rather than discussed in detail. (Reference [14,15])

In humans, sleep-related disorders can lead to various illnesses. Sleep irregularities can cause numerous health problems, including cardiovascular disease, hypertension, glucose irregularities, cancer, depression, and anxiety disorders.[14]

This article selectively examines the effect of the circadian rhythm-cryptochrome relationship on metabolism, summarizing its connection with diabetes. Psychiatric disorders associated with this relationship are addressed in the subsequent section.

In mammals, the CLOCK and BMAL1 transcription factors regulate the central oscillator in the hypothalamus and even in peripheral tissues; however, the connection between cellular rhythms and organismal homeostasis, including the stability of energy and fuel utilisation cycles, remains unresolved. In humans, one of the most important physiological characteristics is the daily variability of glucose tolerance and insulin sensitivity throughout the 24-hour day. More importantly, disruption of the circadian oscillation of glucose metabolism can cause type 2 diabetes. [5] Biological clocks located in the structure of the pancreas regulate the secretion of metabolism-related hormones (This detail is not covered in this article see reference [5]).

C. The effects of circadian rhythms and cryptochromes on human psychology

As I mentioned previously, the sleep-wake cycle has very important effects on human health. One of these effects is on mental health. As I mentioned in the previous section, the sleep-wake cycle plays a role in regulating many activities in the human body. As a result, the changes that occur in our bodies affect our mental health.

This article provides a summary of mental illnesses; no details are given. (For more information, see reference [1])

The most significant factor disrupting the sleep-wake cycle is light. Nowadays, many people are exposed to artificial light. Artificial light can come from technological devices such as phones and tablets, or from artificial lighting sources.

The first condition I wish to discuss is major depressive disorder (MDD). Major depressive disorder is characterised by mood changes, typically increased sadness and/or irritability, and is accompanied by at least one of the following psychophysiological symptoms: changes in sleep, appetite or sexual desire, loss of pleasure, slowed speech or movement, crying and suicidal thoughts. [1]

MDD relates to countries' levels of modernity. The prevalence of factors disrupting the circadian rhythm (night lighting, shift work, jet lag, etc.) may reflect the interaction between circadian rhythm disorders and other environmental factors. [1]

The second condition I would like to mention is anxiety. Numerous studies suggest that jet lag and night shifts trigger anxiety. A series of studies have been conducted on the relationship between circadian rhythm and anxiety. [1] Findings from studies conducted on mice and hamsters in particular have revealed that behavioural patterns associated with increased anxiety were observed following changes in environmental factors that disrupt the circadian rhythm (such as exposure to light). However, these findings are not discussed in this paper (for more information, see reference [1].

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IV. Conclusions

The relationship between circadian rhythms and cryptochromes has very important effects on living organisms. Changes occurring in living organisms in accordance with the day-night cycle enable them to adapt quickly to changing environmental conditions and thus make the most efficient use of the day. This situation has provided living organisms with an evolutionary advantage.

This relationship has physiological effects in plants, such as flowering and seed production, and in mammals, such as metabolism, fertility, and certain diseases. In addition to physiological effects, this relationship has psychological effects in mammals (especially in humans).

This article represents an interdisciplinary study that addresses the common link between various topics. Explaining this relationship without going into excessive detail has enabled the general readership to better understand the subject and become more knowledgeable about it.

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