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**REVIEW ARTICLE**

# Circadian Rhythms, Biological Clock, and Jet Lag

*Ritmos circadianos, reloj biológico y Jet Lag*

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## ABSTRACT

**Introduction:** succession of days and night that our planet has, made evolve the living beings many years ago, so we have an almost perfect biologic clock prepared to we can adapt without problems to the environmental changes. The suprachiasmatic nucleus deals with it.

**Methodological design:** an integrative bibliographic review of the literature on Circadian Rhythms, biological clock and Jet Lag was carried out. This literature review consisted of a search in SciELO, Google Scholar and PubMed.

The search markers used were: circadian rhythm; internal clock; suprachiasmatic nucleus; Jet Lag. The selection criteria were: articles with free access to the full text, published in Spanish and English.

**Objectives:** describing circadian rhythms and its relation with our internal clock and the Jet Lag like one of the principal disorders.

**Development:** circadian rhythms are physical, mental and behavioural changes that follow a cycle of 24 hours and they respond mostly to light and darkness. These rhythms are regulated by biologic clocks. Our mostly biologic clock is the suprachiasmatic nucleus in the hypothalamus. Jet Lag is the commonest disorders of the circadian rhythm.

**Conclusions:** understanding and respecting circadian rhythms is essential to maintain a balance in our daily routines and promote greater well-being, avoiding the negative effects of jet lag and improving sleep quality.

**Keywords:** Jet Lag; Biological clock; Circadian rhythm; Suprachiasmatic nucleus

## RESUMEN

**Introducción:** la sucesión de los días y las noches que presenta nuestro planeta ha hecho evolucionar a los organismos hace milenios, tanto así que poseemos un casi perfecto reloj biológico preparado para que nos podamos adaptar sin problemas a los cambios ambientales. El núcleo supraquiasmático se ocupa de ello.

**Objetivo:** describir los ritmos circadianos y su relación con nuestro reloj interno y el Jet Lag como uno de los principales trastornos.

**Diseño metodológico:** se realizó una revisión bibliográfica integradora de la literatura sobre los Ritmos circadianos, reloj biológico y Jet Lag. Esta revisión de la literatura consistió en una búsqueda en SciELO, Google Académico y PubMed. Los marcadores de búsqueda utilizados fueron: ritmo circadiano; reloj interno; núcleo supraquiasmático; Jet Lag. Los criterios de selección fueron: artículos con acceso gratuito al texto completo, publicados en español y en inglés.

**Desarrollo:** los ritmos circadianos son cambios físicos, mentales y conductuales que siguen un ciclo de 24 horas, responden principalmente a la luz y a la oscuridad. Estos ritmos se regulan mediante los relojes biológicos. Nuestro principal reloj biológico es el núcleo supraquiasmático, situado en el hipotálamo. El Jet Lag es uno de los principales trastornos del ritmo circadiano.

**Conclusiones:** comprender y respetar los ritmos circadianos es esencial para mantener un equilibrio en nuestras rutinas diarias y promover un mayor bienestar, evitando los efectos negativos del Jet Lag y mejorando la calidad del sueño.

**Palabras clave:** Jet Lag; Núcleo supraquiasmático; Reloj biológico; Ritmo circadiano

## INTRODUCTION

Our planet has very pronounced cyclical characteristics regarding the succession of day and night. It can be said that these factors influenced primitive organisms so that in the course of their evolution they have successfully and precisely developed various chronological mechanisms. Environmental cycles of light and darkness affect living organisms, causing them to develop circadian rhythms adapted to these cycles, most of which are biological. (1)

The discovery of circadian rhythms dates back to the early 20th century, when German scientist Erwin Bünning proposed the existence of an "internal clock" in living organisms that allowed them to synchronize with the daily cycles of light and darkness. (2) However, it was in the 1970s that significant advances were made in understanding circadian rhythms. One of the most important milestones was the discovery of the PER protein in the fruit fly Drosophila melanogaster by American scientists Seymour Benzer and Ronald Konopka. (3)

In the 1980s, American scientist Jeffrey C. Hall and his colleagues conducted experiments with fruit flies and managed to identify the gene responsible for regulating circadian rhythms, which they called "gene period." This discovery was fundamental to understanding how circadian rhythms work at a molecular level. In 2017, Jeffrey C. Hall, along with Michael Rosbash and Michael W. Young, received the Nobel Prize in Physiology or Medicine for their contributions to the field of chronobiology and the discovery of the molecular mechanisms that control circadian rhythms. (4)

Generally, a normal person is awake for approximately 16 hours a day and sleeps for 8 hours, depending on the circadian rhythm. (2) When sunlight activates the suprachiasmatic nucleus (SCN), it projects to the vicinity of the hypothalamus related to body temperature and circadian rhythm, to the pineal gland and to the orexin/hypocretin region.

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As the usual number of hours of sleep approaches, the SCN drive decreases and therefore circadian activity decreases and the homeostatic need for sleep increases. Melatonin is synthesized in the dark. Upon returning in the morning, this need for homeostatic sleep returns to zero and is compensated by SCN stimulation. [3]

This is what makes us think that we have perfectly designed biological clocks that can easily adapt to the ecological cycles of light and darkness and their changes at different times and regions of the planet. For this reason, the following research aims to describe circadian rhythms and their relationship with our internal clock and Jet Lag as one of the main disorders.

## METHODOLOGICAL DESIGN

An integrative bibliographic review of the literature on circadian rhythms, biological clock and Jet Lag was carried out. This facilitated the formulation of global conclusions based on the research analyzed. To carry it out, the following were taken into account: the identification of the topic and the formulation of the guiding question, search in the literature, definition of information to be extracted from the selected studies; critical analysis of the included research and synthesis of knowledge. This literature review consisted of a search in SciELO, Google Scholar and PubMed. The search markers used were: circadian rhythm; internal clock; suprachiasmatic nucleus; Jet Lag.

The selection criteria were: articles with free access to the full text, published in Spanish and English. Duplicates were excluded and those where the scientific quality was low were evaluated through critical reading 31 references of the 38 consulted were used, of which the highest percentage of these are between the last five years and in English and Spanish.

## DEVELOPMENT

Knowledge of the periodicity of natural and environmental phenomena of circadian rhythms dates back very early in human history. The temporal and cyclic variation of biological phenomena on health and disease was very important in the doctrine of ancient doctors. These concepts were collected and developed with the personal observations of Greek naturalists. Aristotle and Galeano wrote about the sleep cycle, focusing on the heart first and the brain second. [5]

Events such as the flowering of plants, the seasonal reproduction of animals, the migration of birds, the hibernation of some mammals and reptiles, phenomena that are currently daily for human beings; In their beginnings, they were considered a simple consequence of the action of astronomical and external factors. According to this opinion held for centuries, the environment imposes its habits on living beings by influencing their circadian cycles. [6]

## Definition of circadian rhythm

In biology, circadian rhythms (from Latin circa, meaning "around" and die, meaning "day") is the oscillation of circadian variables at regular intervals. [6]

All animals, plants and organisms exhibit some form of physiological rhythmic variation (metabolic rate, thermogenesis, flowering, etc.). [5] In all eukaryotes, as well as in many prokaryotes, different rhythms have been observed with periods ranging from seconds to years. Although altered by exogenous cues, these rhythms persisted under laboratory conditions, even in the absence of external stimuli. [7]

Circadian rhythms can also be defined as physical, mental, and behavioral changes that follow a 24-hour cycle. It should be noted that these natural processes are the physiological response to light and darkness, they affect most living beings including animals, plants and bacteria. [7] Chronology is the study of circadian rhythms. An example of a light-related circadian rhythm is sleeping at night and being awake during the day. [8]

## Definition of biological clock

A biological clock is an organism's natural timing device that regulates the cycle of circadian rhythms. They are made up of specific molecules (proteins) that have the ability to interact with cells throughout the body. Almost all tissues and organs have a biological clock. Currently, the same genes that make up the molecular components of the clock have been identified in: humans, fruit flies, mice, plants, fungi and many other organisms. [9]

The brain's master clock coordinates all the biological clocks of a living organism, keeping them synchronized. In vertebrate organisms, including humans, the main clock is a group of about 20,000 neurons that together constitute a structure called the suprachiasmatic nucleus or SCN. The SCN is located in the hypothalamus and receives data directly from the eye. [10]

The internal mechanism of a living organism that allows it to orient itself in time is known as the circadian clock. Of course, it is not a movement that shows the hours and seconds, but a set of organic functions linked to rhythms of life. The same means that as noon approaches, we begin to feel hungry anticipating that it will be lunch time. The same thing happens when night falls, when we start to sleep. [11]

The function of the biological clock is to temporally align different organic activities. This order involves the development of cycles (for example, making ourselves hungry or sleepy every hour). The secretion of glands, the regulation of body temperature and even the activity of the heart and brain, among other organs, depend on the clock. (12)

The actions of our daily lives and the decisions we make can sometimes trigger changes in the biological clock, giving rise to a wide variety of imbalances. People who do not follow a regular eating schedule or those who live at night and sleep during the day experience many inconveniences due to altered biological clocks: chronic fatigue, loss of appetite, depression, etc. (13)

To ensure the proper functioning of the biological clock, the ideal is to maintain a daily routine of rest, physical activity and nutrition. This can help improve the functioning of the body. According to research by some experts, lack of sleep can even contribute to diseases such as cancer, type II diabetes, obesity, heart complications, and various infections. (14)

## Circadian system functioning

Light information is sent by retinal ganglion cells through the optic nerve (ON) to the lateral geniculate nucleus (LGN) and then to other regions involved in the formation of visual images. However, several studies have concluded that certain axons of an unknown group of cells send "non-visual" light information to brain centers that are also involved in visual processing. (15)

Until recently it was known that there were two types of photoreceptors, rods and cones, but in 1923 it was discovered that a third photoreceptor was also involved in the pupillary reflex and other visual responses to stimuli of wavelengths that did not correspond to the of the cones and rods. (16)

In addition, there have been known cases of alterations in the circadian system and suppression of melatonin secretion in blind subjects lacking cones and rods, so it is assumed that there must be another type of photoreceptor beyond the cones and rods that the patient may present. New photopigment, called melanopsin. These cells are the intrinsic photoreceptor retinal ganglion cells (ipRGCs). (17) The melanopsin absorption spectra of ipRGCs were found to be close to the 480 nm peak, and with respect to their optical conduction, there are some differences between cones and ipRGCs. (18)

The ipRGC pathway begins with a photon that reaches the retina and is captured by retinal ganglion cells that contain a pigment called melanopsin, making them inherently sensitive to light. A series of very specific physiological changes occur, which mainly cause the entry of Ca+ ions through the transient receptor potential channels, thus inducing depolarization. (18) Melanopsin is capable of recovering its active conformation; its dynamics are simply by absorbing a second photon with a longer wavelength. (19)

The axons of the ipRGCs send neural and humoral messages to different regions of the brain. The most important connection is that of the SCN through the pathway from the retina to the hypothalamus. The peripheral oscillator is part of the ipRGC pathway, which is located in our bodies under the control of NSQ. These oscillators may be out of sync with your circadian rhythm due to poor diet, late plane travel (Jet Lag), or shift work. (18)

The SCN and oscillator are responsible for the daily rhythms found in most physiological and behavioral functions, and these rhythms, in turn, provide information that can alter the function of the SCN and the oscillator itself. Melatonin production occurs when the SCN sends the order to synthesize to the pineal gland: the SCN projects to the paraventricular nucleus (PVN), and this in turn to the preganglionic neurons of the spinal cord. (18)

Preganglionic neurons innervate the superior cervical ganglia and these in turn innervate the pineal gland and thus induce the synthesis of melatonin. Melatonin is not stored biologically, but is secreted directly into the bloodstream, crossing the blood-brain membrane once synthesized and causing circulating melatonin levels to vary throughout the day and be higher at night, since the postganglionic neurons of the the upper cervical ganglia stimulate the synthesis of melatonin in the pineal gland in the absence of light information. (20)

There is evidence of the presence of this molecular clock in mammals, since numerous studies indicate the existence of neural pathways between the SCN and the heart, liver, pancreas, thyroid and pineal glands. This core can activate or deactivate different pathways depending on the function needed throughout the day, acting as a conductor. (21)

## Does the body produce and maintain its own circadian rhythms?

Certainly, in our body there are natural factors that have the ability to create circadian rhythms. For humans, some of the most important genes in this process are periodic and coding genes, which code for proteins that accumulate in the cell nucleus at night and decrease during the day. (22)

Studies in fruit flies indicate that these proteins help trigger feelings of alertness, alertness, and drowsiness. However, environmental cues also affect circadian rhythms; For example, when exposed to light at a different time of day, the time when the body activates the cycle and crypt genes can be reset. (22)

In 2017, a group of researchers in the United States made up of Jeffrey C. Hall, Michael Rosbash and Michael W. Young received the Nobel Prize in Medicine and Physiology in recognition of their research on circadian rhythms. By studying fruit flies, which are genetically similar to humans, they isolated a gene that helps control the circadian clock. Scientists have shown that this gene produces a protein that builds up in cells at night and then breaks down during the day. This process can affect sleep, the acuity of brain function and more. (23)

**Types of circadian rhythm disorders include the following:** (24)

**1) Phase advancement:** Over time, especially after age 60, people begin to exhibit a very specific pattern of sleep hours, generally falling asleep earlier than before and therefore also waking up.

**2) Phase delay:** it is a syndrome characterized by the inability to start sleeping at the usual or desired time, as well as the difficulty in getting up in the morning and complying with the schedule imposed by obligations. When continuing to sleep is not an option, this leads to a decrease in sleep time.

**3) Irregular sleep-wake rhythm:** this is a very disordered distribution of sleep and wake times over 24 hours. While total sleep duration is generally normal, the problem is that it is fragmented and scattered throughout the day and night, which negatively affects daytime performance.

Some of the state changes that people typically experience over the course of a day: (25)

6:00 to 8:59: This is the perfect time to get out of bed. For men, this is the time when their testosterone levels peak. On the other hand, that is the time when the heart is most susceptible to cardiac arrest, because its vessels are more rigid and less flexible than the rest of the day, blood pressure is maximum and blood is very thick. (25)

From 9:00 to 11:59: During this time, our short-term memory works better than ever and our brain can process information with exceptional intensity. This gets special attention since cortisol (the stress hormone) is at an all-time high. (25)

From 12:00 to 14:59: at this time it is normal to eat, which is why stomach activity increases, alertness decreases and statistically the rate of traffic accidents is the highest. (25)

3:00 p.m. to 5:59 p.m.: Core temperature spikes, heart and lungs work better than the rest of the day and is a good time for physical activity, such as exercise. (25)

From 6:00 p.m. to 8:59 p.m.: This is the ideal time to have dinner, although it is not advisable to eat too much because it can increase the risk of diabetes and obesity. This is also the right time of day to develop intuitive thinking and, due to the peculiarities of our circadian clock, our liver metabolizes alcohol. (25)

From 9:00 p.m. to 11:59 p.m.: the internal temperature of the body drops and we begin to produce melatonin, a hormone that helps us fall asleep. (25)

From 00:00 to 02:59: attention and vigilance are minimum, while melatonin is maximum. On the other hand, the brain begins to consolidate our memories and discard the unnecessary. (25)

From 3:00 to 5:59: decreases body temperature and increases the risk of asthma attacks and natural births. (25)

## Jet Lag

Jet lag, also known as rapid time zone syndrome, transoceanic syndrome, circadian rhythm disorder, time zone syndrome or simply Jet Lag, is an imbalance created between a person's internal clock (it marks the hours of sleep and wakefulness). ) and the new hours that are established when traveling a lot. Distances, across different time zones, or people living in countries that change time in summer and winter during the day and night will maintain a state of surveillance. (26)

## How is circadian rhythm related to time zone latency?

When crossing different time zones, the biological clock will be different from the local time; For example, if you fly from the east from California to New York, you "lose" three hours. When you wake up at 7am on the East Coast, your body clock will still be on the West Coast, so it will seem like 4am to you. The biological clock will reset, but it will work at a different speed. It usually takes a few days to adjust to the new time zone. Adjusting after the “gain” period may be a little easier than after the “loss” period, because the brain adjusts differently in the two situations. (27)

Among the symptoms that Jet Lag can cause are: (28)

- Generalized fatigue is the most common symptom; the person feels less confused when going west because doing so prolongs the experience of the circadian clock and is less likely to distort the day-night cycle. However, if we go east, that means going against the biological clock.
- Conditions in the digestive system: vomiting.
- Confusion in decision making or speech.
- Lost memory.
- Irritability and apathy.

Those in treatment who require scheduled medications should consider the need to modify them as prescribed by their doctor to compensate for circadian rhythm disturbances; Therefore, it may be necessary to change the insulin dose and schedule depending on the number of time zones crossed, time spent at each destination, diet and activity, so blood glucose should be measured frequently. (29)

Treatment regimens may need to be modified based on time savings rather than local time. Some research suggests that vigorous exercise early in the morning on the first day after a time difference can speed adjustment to the new schedule better than gentle or melatonin treatments. (29)

The impact of jet lag can be minimized by taking the following steps before, during and after the flight: (30)

**1) Before takeoff:** Passengers should be advised to rest, exercise and eat a healthy diet. When a person is in good shape, they may not suffer the impacts of Jet Lag very strongly. You should also consult with your doctor to plan what medical behaviors to monitor, including medications or any other necessary details. Another tip is to adapt the time zone of the destination in advance. It may be effective to perform daily routines an hour before or after, three to four weeks before departure. (30)

**2) During the flight:** To avoid dehydration, passengers should be advised not to drink alcohol or caffeine. Caffeine not only causes dehydration, but also disrupts sleep. Instead, the recommendation is to drink plenty of water to help counteract the effects of the dry environment inside the plane. Passengers are encouraged to exercise their legs while seated and move around the aircraft when the seat belt signal is activated, every one to two hours. One option to combat time zone lapses is to take smaller routes if they are too long and spend the night in the city. And finally, try to match your flight's sleep time to your destination. [30]

**3) After landing:** A useful way to reduce jet lag is to adjust to local time. Likewise, sun exposure during the day is effective and useful. [31]

## CONCLUSIONS

Understanding and respecting circadian rhythms and the biological clock is vitally important to maintain a proper balance in our daily routines and promote greater general well-being. These rhythms regulate various physiological functions and affect our quality of sleep, metabolism and mood. When circadian rhythms become imbalanced, as happens in Jet Lag, negative effects are experienced on the patient's health and well-being. Therefore, it is essential to take measures to minimize the effects of Jet Lag and adapt to local time when traveling.

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## AUTHORSHIP CONTRIBUTION

**MOCM:** conceptualization, research, methodology, writing of the original draft.

**LHC:** research, writing of the original draft.

**AMG:** methodology, resources, supervision

**OJER:** research, writing of the original draft.

## CONFLICT OF INTERESTS

The authors declare no conflict of interest.

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