UNIVERSIDAD DE SEVILLA

FACULTAD DE FARMACIA

“FACTORS AFFECTING THE CIRCADIAN RHYTHM: TOXICOLOGICAL PERSPECTIVE”

Alexander Gawn Martínez

UNIVERSIDAD DE SEVILLA
FACULTAD DE FARMACIA

TRABAJO FIN DE GRADO

GRADO EN FARMACIA

“FACTORS AFFECTING THE CIRCADIAN RHYTHM: TOXICOLOGICAL PERSPECTIVE”

Revisión bibliográfica

Departamento de Nutrición y Bromatología,
Toxicología y Medicina Legal
Sevilla, julio de 2022

Estudiante: Alexander Gawn Martínez
Tutora: Ángeles Mencía Jos Gallego

ABSTRACT

Since the beginning of animal evolution, adaptation to the environmental factors has been key to survival in order to maintain the continuity of the species. Therefore, numerous physiological mechanisms developed over the years to overcome adversities to the point where living organisms learnt to anticipate them through an internal biological clock: the circadian rhythm. Its discovery opened a new dimension of study in the scientific field with more and more researchers gaining interest about this subject up to the present day. It has been found that this internal rhythm is entrained by both internal and external factors and is responsible for the synchronization of all physiological processes through peripheral clocks, where the main pacemaker, the suprachiasmatic nucleus (SCN), is located in the hypothalamus. The SCN releases neurotransmitters that orchestrate the rest of the system acting in different target tissues, but recent studies showed that a deeper level of control governed the protein synthesis: the genetic molecular level. This means that our genetic material contains clock genes that regulate the biological clock. The goal of this work is to describe the main factors that negatively affect in different ways the correct function of the circadian rhythm, leading to health issues due to the chronodisruption and the consequent metabolic disorder. These can act in a wide range of situations, being classified as environmental, behavioural, intrinsic and iatrogenic factors. Finally, taken the fact that in modern life we're constantly exposed to many of these factors, some ideas are exposed about the application of this knowledge into people's lifestyles and into vital aspects such as pharmacological therapy, technological and chemical industry, etc which seek to protect and even promote human beings' health.

KEYWORDS

"Circadian rhythm", "suprachiasmatic nucleus", "chronobiology", "health", "toxicology"

INDEX

1. INTRODUCTION

1.1. HISTORICAL CONTEXT

From the beginning of human existence, we've evolved and learned to adapt to environmental phenomena such as sunlight and temperature changes, as well as any other circumstances surrounding us that have followed a constant pattern such as hunting, eating and mating hours. This means that at certain moments each day we were readier to fulfil different tasks more than others, increasing our success rate and ultimately the chances of survival for our species.

What's interesting about these biological rhythms is that after centuries of repeating the same series of daily events, they become predictable. In other words, our circadian rhythm doesn't exist to help us adapt to the environment, but instead it serves as a mechanism that's designed to anticipate changes and overcome adversity. As a result, it has played a major role in human survival ensuring our existence to date despite the many important changes that have occurred along time. Studies have shown that our metabolic parameters change one way or another depending on the time of day making us more prone to sleep, eat, do exercise or even to mate at specific moments throughout each day due to this genetic adaptative mechanism (Figure 1).

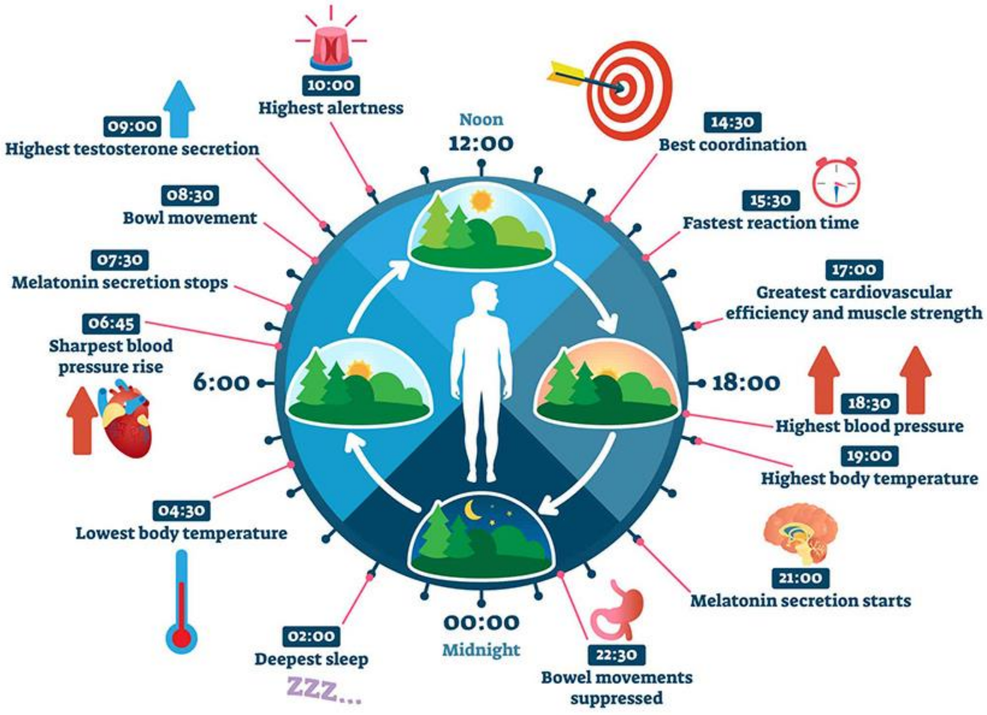


Figure 1. Representation of the circadian metabolic rhythm as a clock with highlights of the most relevant physiological body functions (Kelly 2020).

The first person to take notice of this phenomenon was the botanist Charles Linnaeus in the 18th century. He observed during his morning walks that some plants' petals opened earlier than others and some closed in the evening or at night, naming this behaviour as the "sleep of plants". This way, he designed a clock in which the hour of maximum opening of petals was detailed for each species of plants, thus the name "flower clock" (Figure 2).

Figure 2. Linnaeus' flower clock (Patowary 2019).

However, it wasn't until 1729 when the first scientific evidence of the circadian rhythm was made by the astronomer Jean-Jacques d'Ortous de Mairan. It was on a summer evening while working at his desk that he spotted a *Mimosa pudica* plant that had closed its leaves and asked himself what the cause of this movement was, immediately jumping to the conclusion that it may be caused by the changes in sunlight. So, the next day he placed it in the basement and kept it in complete darkness for 24 hours, only to find it to his surprise with its leaves open the next morning despite being isolated from sunlight for one full day. It turned out that it wasn't the sunlight or the environmental factors that induced the movement of its leaves. It had to be an internal clock within the plant that acted independently of the exterior even without the usual stimuli that were believed to be necessary to activate or synchronize its functions (Figure 3).

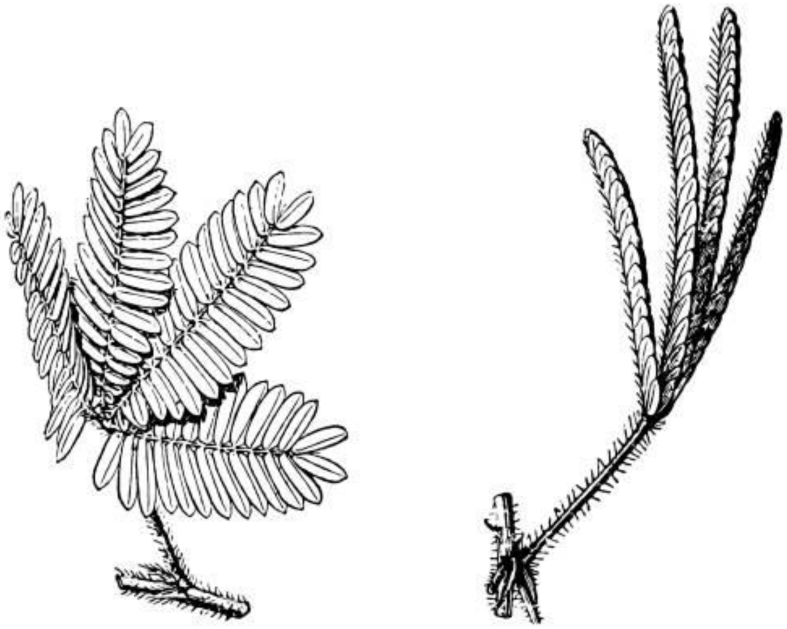


Figure 3. On the left, *Mimosa pudica* with its leaves open. On the right, the same plant with its leaves closed. This change of stadium takes place every day, remaining open during the day and closed during the night. This is a defence mechanism against predators because when closed, it resembles a dried plant. Moreover, it helps preventing it from losing too much water or to protect itself from the wind, reducing its surface area (Garaulet, 2017).

Since then, numerous scientists all over the world have been researching this new paradigm called “Chronobiology”, among which some deserve to be mentioned such as Colin S. Pittendrigh (for his discovery of the basic principles of biological rhythms through his study of the fruit fly *Drosophila melanogaster*), Julien-Joseph Virey (who wrote his thesis about the daily changes and periodicity of its phenomena in health and diseases), and so on (Garaulet, 2017). Thanks to the work of all these researchers, it’s become very clear that the living organisms' behaviour is governed by an internal clock that has a period shorter or longer than a day (hence the name “circa” which means around and “diem” meaning one day) (Merrow et al., 2005).

1.2. STRUCTURE & PHYSIOLOGY

In mammals, the main structure responsible for the circadian timing system (CTS) is the suprachiasmatic nucleus (SCN), located in the hypothalamus (Figure 4). The SCN is a self-sufficient pacemaker that regulates peripheral clocks found throughout the body (even cells have their own operating independently, but they're able to coordinate with each other forming a single rhythm for a specific tissue or organ in a hierarchical organisation) (Honma, 2018).

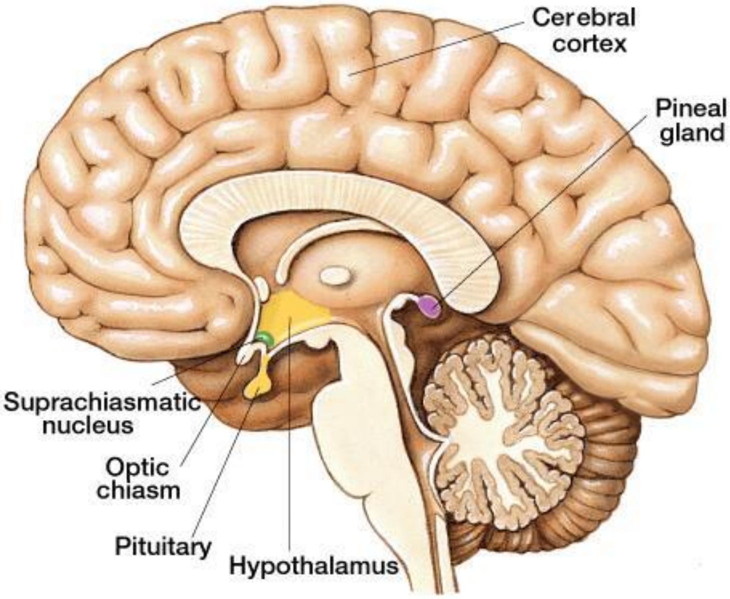


Figure 4. Anatomy of the human cranial central nervous system, revealing the location of the suprachiasmatic nucleus, right above the optic chiasm (thus its name). It is closely related to the pineal gland, responsible for the release of melatonin hormone which induces sleep (Obot 2014).

Recently, it's been discovered that the SCN is divided into two different sections known as the "core" and "shell" subnuclei. Each of these releases a series of unique neuropeptides towards a specific target, only having in common the inhibitory neurotransmitter gamma-aminobutyric acid (GABA). In the core, along with the already mentioned GABA, are the neuropeptides vasoactive intestinal polypeptide (VIP) and gastrin-releasing peptide (GRP); whereas in the shell, on the other hand, neurons contain along with GABA arginine vasopressin (VP). This anatomic configuration implies that the information flows from core to shell, being originated in three afferent systems that converge in the SCN core: the retina, which contains the excitatory neurotransmitter glutamate (GLU) as well as the neuropeptides substance P (SP) and pituitary adenyl cyclase–activating peptide (PACAP); the intergeniculate leaflet of the thalamus (IGL), where neuropeptide Y and GABA can be found; and the mesencephalic raphe nuclei, with 5-hydroxytryptamine (5-HT; serotonin). Beyond the already mentioned, there are other afferent systems that converge this time in the SCN shell: these are the basal forebrain (BF) and pons, containing acetylcholine (ACh); the medulla, responsible for releasing norepinephrine (NE); and the posterior hypothalamus (Post hyp), in which histamine (HA) can be found (Figure 5) (Moore, 2013).

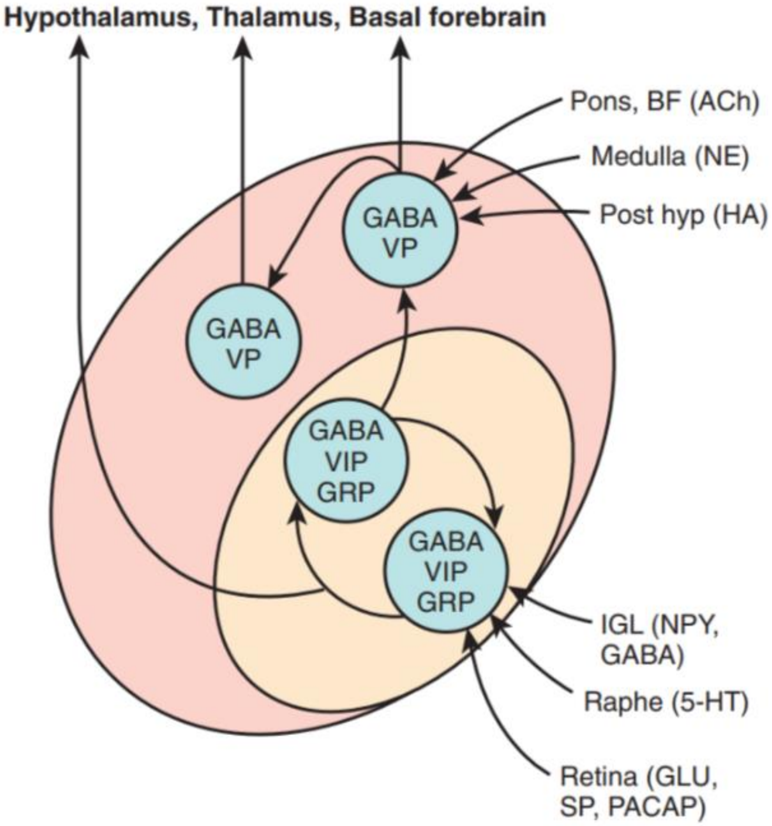


Figure 5. Anatomic organization scheme of the suprachiasmatic nucleus (SCN), showing the two main parts (core, in yellow, and shell, in orange) and the afferent system that comprises it, along with the protein products that will engage with the necessary targets to regulate several metabolic body functions (Rosenwasser and Turek, 2010).

Although it was believed through evidence obtained from early studies that clock signals were generated by protein synthesis, in the past decade a new discovery has changed the way of understanding the circadian rhythms that govern our entire metabolic system: the genetic molecular level. This means that our genetic material is configured by genes that orchestrate the protein synthesis responsible for the correct function of our biological clock. The first mammalian clock gene that was found was called "Clock" (Clk), whereas other homologous genes later discovered were three "Period" genes (Per1, Per2, Per3), Tim, Bmal (B), Ck1e, as well as two cryptochrome genes (Cry1 and Cry2), all of which are expressed in the suprachiasmatic nucleus' neurons. In addition to the previously mentioned, transcription of a great number of "clock-controlled genes" (CCGs) takes place giving timing signals to a wide selection of cellular processes (Figure 6) (Rosenwasser and Turek, 2010).

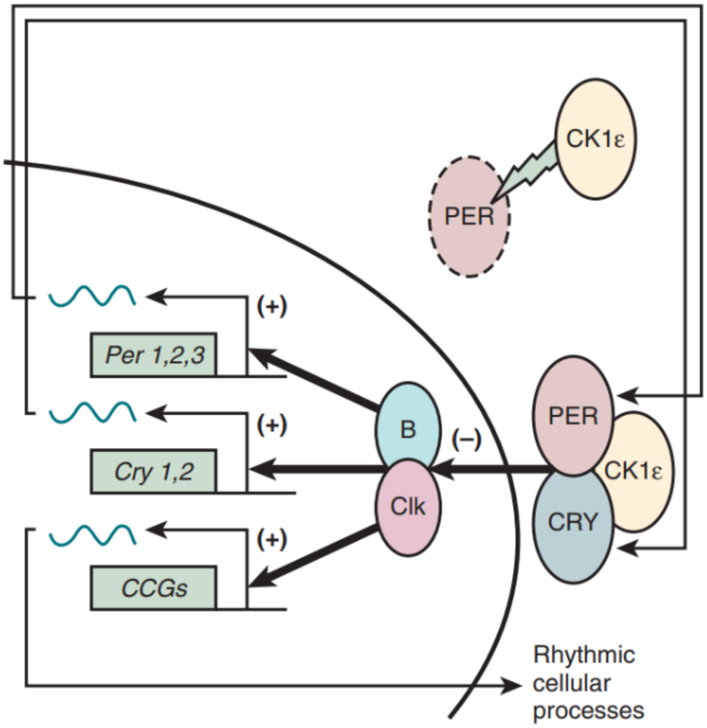


Figure 6. Diagram representing the different clock genes involved in the circadian rhythm, several of them forming heterodimers promoting the transcription of others, creating both positive and negative feedback loops in order to maintain the overall stability of the clock (Rosenwasser and Turek, 2010).

Besides the transcription-translation feedback loops that control the circadian rhythm, it's entrained or synchronized by light- dark cycles detected by the retina (which is the light sensitive tissue that resides on the back of the eye) and processed in the form of projections to the SCN. A new type of photoreceptors has been identified not so long ago, in addition to the well-known cones (responsible for the colour vision) and rods (that grant us with night and peripheral vision): melanopsin-containing retinal ganglion cells (mRGCs). The presence of this kind of photoreceptors was spotted due to the observation of blind (coneless and rodless) mice responding to light stimulation through pupil constriction. Further studies confirmed that this kind of receptor is intrinsically photosensitive thanks to melanopsin, a light-sensitive protein, meaning that even blind people are sensitive and adapt to the 24h cycle. Synchronization of the circadian rhythm, pupillary control or regulation of melatonin hormone release are some among its main functions, making it vital for the adjustment of our internal clocks to the external stimuli (Do and Yau, 2010).

But not only our circadian rhythm is externally synchronised by light. It also depends on behavioural factors such as food intake or fasting, as well as physical activity or rest, and even changes in social life. It is believed that while the main clock – the SCN – is adjusted with the outside mainly by light, most of the peripheral clocks (such as body fat, the liver or the pancreas) depend on feeding variations (Figure 7). As a result, the study of the synchrony within and between central and peripheral oscillating systems has aroused more and more interest in the past decade due to the importance it's shown to have in the balance between health and disease (Rosenwasser and Turek, 2010).

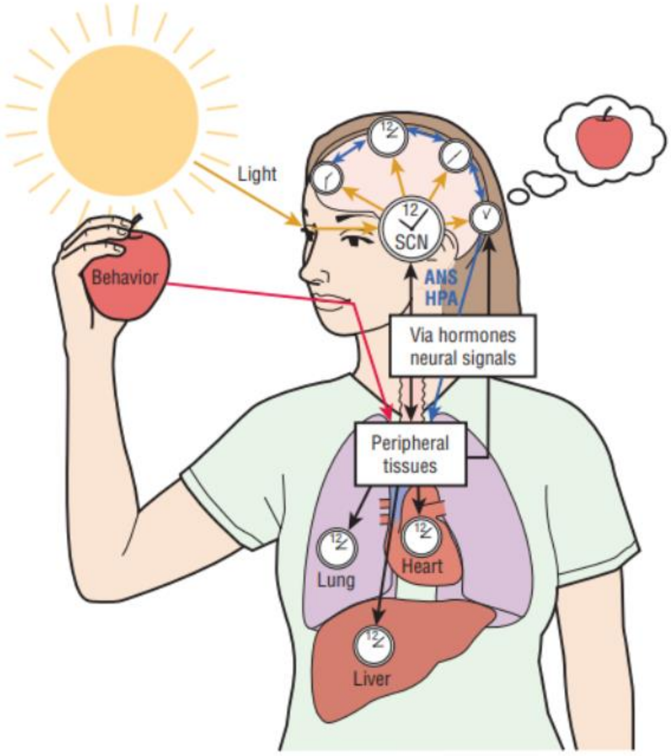


Figure 7. Visual example of the relation between central and peripheral biological cellular clocks as well as the external factors that help synchronise both types. Nevertheless, under non-ideal conditions (such as constant light), weakening of these coupling conditions may overcome resulting in the loss of coherent tissue and behavioural rhythmicity (Rosenwasser and Turek, 2010).

2. OBJECTIVES

The main goal of this bibliographical research is to study the environmental, behavioural, intrinsic and iatrogenic factors that affect the human circadian rhythm from a toxicological perspective and to shed light on the possible negative health consequences produced by of each of them to gain awareness of the importance of taking care of our own biological clocks as more and more scientific evidence proves its relevance in long-term life quality and lifespan.

3. METHODOLOGY

For the realization of this work, several databases such as Science Direct, Google Scholar, PubMed, Biomed Central, etc. were consulted.

Keywords used to search all references are the following: circadian rhythm, sleep disorder, pollution affecting circadian rhythm, melatonin alteration, circadian rhythm eating disorders, suprachiasmatic nucleus, ganglion cells, circadian effect on drug response.

As for the selection criteria, English articles were chosen to find a wider range of information about this subject given that it's still quite recent and the amount of research work about it is quite limited. Also, articles published in the last 5 years were given priority over the older ones as the latter lacked sufficient updated data.

References were organized and cited in the Vancouver format with help from an informatic tool called Mendeley Cite, proposed by the University of Seville.

4. RESULTS AND DISCUSSION

4.1. ENVIRONMENTAL FACTORS

4.1.1. CHEMICAL FACTORS

There have been six main groups identified as negative factors for the circadian rhythm or circadian disrupters. These compounds are organic chemicals, cyanobacterial toxins, neuroactive drugs, polychlorinated biphenyls, biocides and pesticides, metals and steroid hormones, the last two being of more importance than the rest (Zheng et al., 2021).

Studies carried out with zebrafish, which serve as a model organism for fish and mammals, have shown different physiological alterations after being exposed to each type of disrupters. These operate altering core circadian genes that in turn, regulate biological processes, making them relatable to the disrupters that are consequently responsible for any health issues caused by the misadjustment of the circadian system.

Steroid hormones, for instance, are comprised of several groups according to their molecular structure. One of them are glucocorticoids, which are essential for the regulation of circadian rhythms and physiological pathways associated with them (Dickmeis, 2009). A lack in corticotrope pituitary cells causes diminution of cell proliferation cells, although it doesn't alter gene expression. This implies that mutations modifying them or even contact with exogenous glucocorticoids (such as dexamethasone and cortisol) can have a negative impact on biological processes like behavioural activity and melatonin levels (Zhao et al., 2018). Another important group is the progestins, where a two-week exposure to progesterone has shown to be responsible for transcriptional modifications affecting regulation of cell cycle, apoptosis and genes related to reproduction (Zucchi et al., 2014). Lastly, natural and artificial oestrogens only pose a risk in reproduction (Liang et al., 2019). Comparison between different classes of steroid hormones showed that glucocorticoids were the most effective and androgens the only ineffective ones for alterations in transcription and behaviour.

Metals are also very important, specially transition metals. For example, lithium, in a long-term exposure, slows down locomotor activity, modifies melatonin receptor's expression and tissue growth and regeneration are limited (Xiao et al., 2017). Another metal that has an impact on the circadian rhythm is copper, which after time has shown to affect reparation of DNA, cell development, oxidative stress and physiological processes (Vicario-Parés et al., 2018). As for cadmium, changes in proteolysis and amino acid metabolism and autophagy were observed, as well as in behaviour strength (Yang et al., 2018). Finally, lead has been found to cause circadian variations of several neurotransmitters in the brain (Spieler et al., 1995).

To date, just a few pesticides and biocides have been studied. Thifluzamide, which is a fungicide used frequently in the treatment of diseases in rice, has been proved to lower growth hormone (GH) and dopamine levels and mRNA gene levels associated with development, behaviour and synthesis of steroid hormones, causing inhibition embryonic development (Yang et al., 2019a). Flutolanil, also a fungicide, serves for fighting cereal diseases, and exposure produces increased levels of melatonin and decreased levels of GH, responsible for abnormal development of the embryo and sudden movements (Yang et al., 2019b). Climbazole is another fungicide that can be found in products used for personal care, and it's been found to limit oocyte maturation and production of steroids leading to irreversible virilization (Zhang et al., 2019). Finally, the herbicide atrazine is a circadian disrupter that stimulates lipid peroxidation disrupting the metabolism of the liver, as well as it was reported to weaken physical activity and delay periodicity of the circadian rhythm for one hour (Yang et al., 2018).

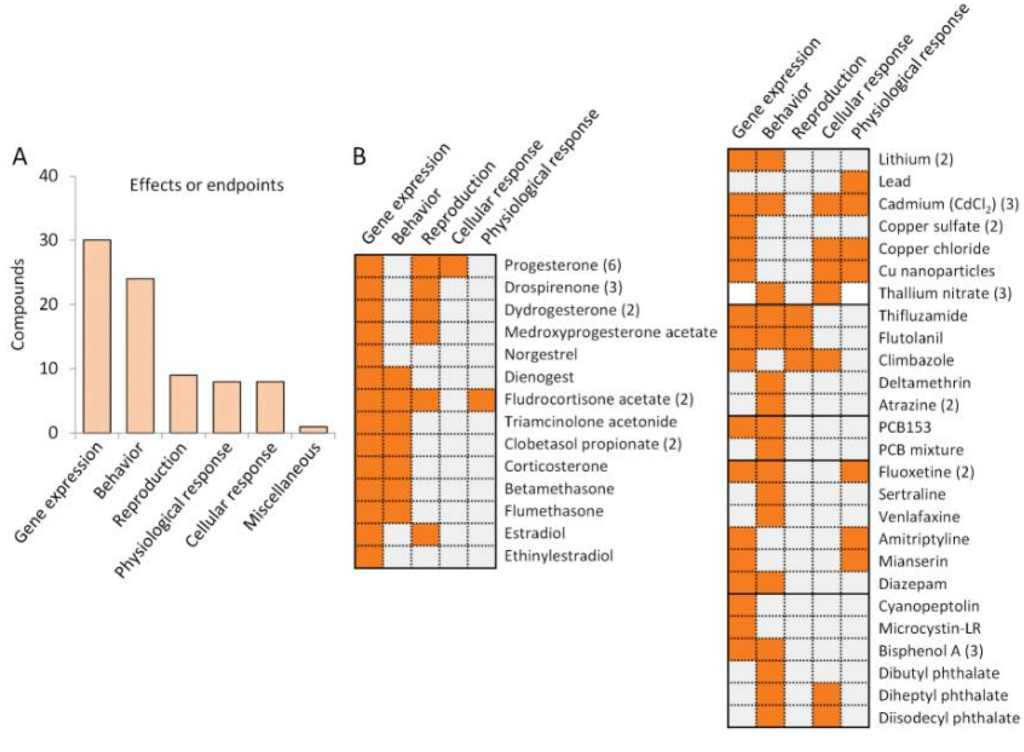
Another type of disrupter compounds are polychlorinated biphenyls (PCBs). As a manifestation of industrial activity, they are known to be neurotoxic, immunotoxic and cancerogenic, causing metabolic and developmental disorders (Aluru et al., 2020).

Water polluted by neuroactive drugs such as antidepressants represents a threat to the normal functioning of the circadian rhythm. Exposure to venlafaxine has showed a behavioural change with diminution of daily activity (Parrott and Metcalfe, 2017). Diazepam, an anxiolytic widely used, was discovered to induce transcriptional alterations in circadian genes causing alterations in locomotor behaviour (Oggier et al., 2010).

Inside cyanobacterial toxins, microcystins have been a threat to living organisms by presenting negative effects on regulation of liver circadian rhythm and physiological processes like amino acid and lipid metabolism, as well as on energetic production (Qiao et al., 2016). A different cyanobacterial toxin is cyanopeptolin (CP1020) which exhibited harmful influence on molecular pathways such as the circadian rhythm, DNA damage and reconstruction and reaction to light (Faltermann et al., 2014).

The last circadian disrupter group is that of organic chemicals. Bisphenol A (BPA) has been found to modify circadian genes' expression and alter behaviour (Choi et al., 2018). As for phthalates, another type of organic chemical used as plasticizer, they were identified to present toxicity in reproduction and lipid peroxidation, and to weaken behavioural strength (Poopal et al., 2020).

All the information above indicates that the empirical results obtained with fish is susceptible of being translated into human circadian rhythm. This is because most if not all the physiological mechanisms in both species are the same. However, knowledge about all the environment chemical factors is still very limited, and it's yet unknown how and with what intensity they alter the regulation of circadian rhythms in mammals and humans (Figure 8) (Zheng et al., 2021).



Gene expression	Behavior	Reproduction	Cellular response	Physiological response	
🟧		🟧	🟧		Progesterone (6)
🟧		🟧			Drospirenone (3)
🟧		🟧			Dydrogesterone (2)
🟧		🟧			Medroxyprogesterone acetate
🟧					Norgestrel
🟧	🟧				Dienogest
🟧	🟧	🟧		🟧	Fludrocortisone acetate (2)
🟧	🟧				Triamcinolone acetonide
🟧	🟧				Clobetasol propionate (2)
🟧	🟧				Corticosterone
🟧	🟧				Betamethasone
🟧	🟧				Flumethasone
🟧		🟧			Estradiol
🟧					Ethinylestradiol

Gene expression	Behavior	Reproduction	Cellular response	Physiological response	
🟧	🟧				Lithium (2)
				🟧	Lead
🟧	🟧		🟧	🟧	Cadmium ($CdCl_2$) (3)
🟧					Copper sulfate (2)
🟧			🟧	🟧	Copper chloride
🟧			🟧	🟧	Cu nanoparticles
	🟧		🟧		Thallium nitrate (3)
🟧	🟧	🟧			Thifluzamide
🟧	🟧	🟧			Flutolanil
🟧		🟧	🟧		Climbazole
	🟧				Deltamethrin
	🟧				Atrazine (2)
🟧	🟧				PCB153
	🟧				PCB mixture
🟧	🟧			🟧	Fluoxetine (2)
	🟧				Sertraline
	🟧				Venlafaxine
🟧				🟧	Amitriptyline
🟧				🟧	Mianserin
🟧	🟧				Diazepam
🟧					Cyanopeptolin
🟧					Microcystin-LR
🟧	🟧				Bisphenol A (3)
	🟧				Dibutyl phthalate
	🟧		🟧		Diheptyl phthalate
	🟧		🟧		Diisodecyl phthalate

Figure 8. Summary of chemical agents and their effects on circadian genes at several physiological levels: On the left (A) there is a chart representing the number of chemicals that have been reported to have each of the effects observed; on the right (B), a table with different examples of each group where it's possible to contrast the different effects of each disrupter with the rest (Zheng et al., 2021).

4.1.2. PHYSICAL FACTORS

Arguably the most important physical factor that regulates the circadian system, is light. As explained in the introduction of this work, the light/dark (LD) cycle serves as the principal zeitgeber for the circadian system by regulating through visual stimulation the main pacemaker, the SCN. This means that any disturbance of normal stimulation can disrupt internal rhythms and have health consequences (Potter et al., 2016). In this case, it can either be caused by lack or excess of light.

In the first case, lack of daylight can have some negative effects on the circadian system since exposure to daylight brings behavioural and physiological benefits. In modern society, most of the population is sheltered from light almost completely and only spend 1-3 hours outdoors daily, which contributes to low vitamin D levels (Diffey, 2011). Despite the importance of LD cycles, vitamin D also plays a role in regulation of the circadian rhythm. Vitamin D is synthesized thanks to UV-B irradiation, and it participates directly in the transcription of clock genes in vitro, making it plausible that there is a relation between health and Vitamin D status (Figure 9) (Theodoratou et al., 2014).

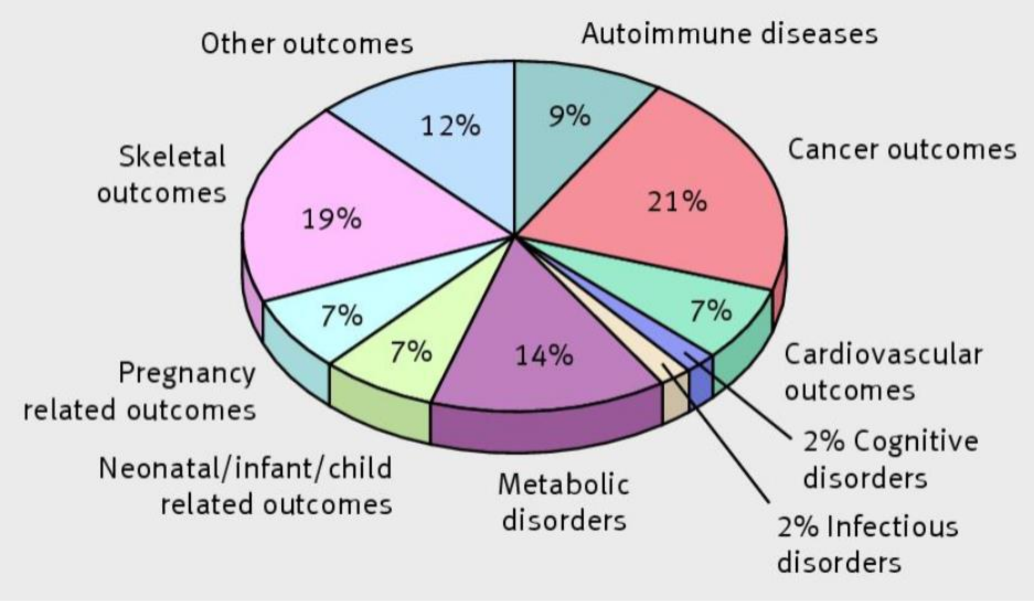


Figure 9. Health consequences related to vitamin D proportionally organized in different categories (Theodoratou et al., 2014).

On the contrary, excess of light has become a problem since the existence of artificial light. Study shows that over 75% of world's population is affected by it at night (Cinzano et al., 2001). It's also estimated that artificial light intensity more than doubles daylight's during night affecting individuals' sleep-quality (Wright et al., 2013). With recent technology's advances, more interesting electronic products are made and with them nighttime light exposure is increased. Some of these even emit monochromatic blue light, and because ganglion cells in the retina are photosensitive, it stimulates them at times they shouldn't be, supressing melatonin synthesis at night and thus facilitating circadian clock and sleep disruption (Chang et al., 2015). Another relation found was that between artificial light and obesity prevalence, being a person more likely to become overweight if exposed to light during nighttime (Rybnikova et al., 2016).

Regarding temperature, which is one of the most important external cues after light, it has a relevant influence over metabolic homeostasis. For instance, studies have concluded that chronic exposure to temperatures under thermoneutrality (26ºC) increases body temperature rhythm amplitude (Refinetti, 2020). Given that peripheral tissues can create oscillations after being externally stimulated, temperature variations can serve as a powerful zeitgeber to restart these tissues' biological clock. Therefore, thanks to experiments carried out with mice, evidence has been shown that external temperature synchronises feeding behaviour and oscillation of metabolic and circadian gene expression in the liver. Although further research needs to be done to discover to full length the effects of this parameter on the circadian rhythm, it's clear that temperatures outside thermoneutrality can lead over time to physiological stress and ultimately to health issues due to maladjustment of the circadian system (Rabearivony et al., 2020).

4.1.3. ELECTROMAGNETIC FACTORS

Apart from the factors already mentioned, the circadian rhythm can also be altered by ultraviolet wavelengths and by electromagnetic fields to which people are exposed in everyday life. These effects vary according to the potency of the electromagnetic fields and to the size of each individual (Contalbrigo et al., 2009).

Ultraviolet wavelengths were found to be responsible for limiting melatonin concentration in the pineal gland at night (Figure 10) (Podolin et al., 1987).

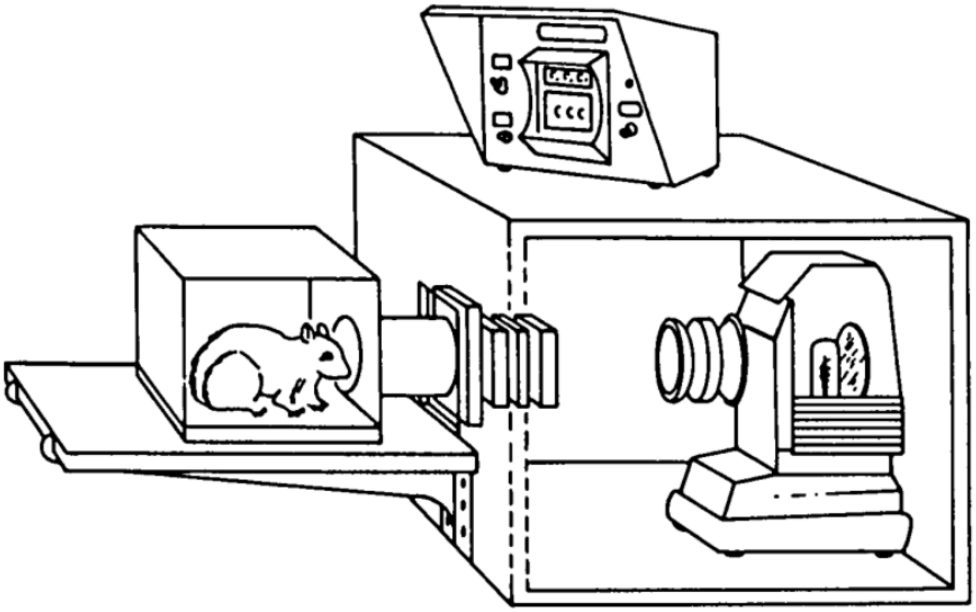


Figure 10. Experimental chamber used to study the effects of UV light on Syrian hamsters' melatonin secretion (Podolin et al., 1987).

Regarding electromagnetic fields, there are two types to be considered: extremely low frequency electromagnetic fields (ELF-EMF) and extremely high frequency electromagnetic fields (EHF-EMF).

ELF-EMFs usually come from high-voltage line and electrical appliances used at home and in workspaces, and it's been discovered that they increase the chances of having cancer (Kumlin et al., 2005; Stelletta et al., 2007), depression, and miscarriages (Dasdag et al., 2002).

On the other hand, EHF-EMFs, specifically radiofrequency electromagnetic fields (RF-EMF), are used in many wireless broadcast utilities like radio, TV, mobile phones, etc. also used in domestic and work environments. In the modern era, mobile phones are the best example of devices to which humans are exposed as they carry one with them everywhere most of the time, making them a big threat to their health as studies show evidence of the relation between mobile usage and its health effects (mainly cancer) (Kundi et al., 2004).

4.2. BEHAVIOURAL FACTORS

4.2.1. SLEEP

Sleep is a body and metabolic state of rest and lower consciousness that repeats itself every day with positive effects on humans' and animals' health such as memory development and the strengthening of the immune system (Lange et al., 2010; Mignot, 2008). It's interesting that sleep is entrained by circadian rhythms and vice versa (Danilenko et al., 2003).

However, alteration of normal sleep patterns can cause negative health consequences due to anormal hormone concentrations and weak immune functionality (McEwen, 2006). One of the main causes responsible for this anomaly is nocturnal shift working, which in long term deteriorates mental performance, well-being and ultimately, health. Many studies have concluded that it increases the chances of having cancer and rheumatoid arthritis (Haus and Smolensky, 2006).

4.2.2. FEEDING

There are different chronotypes depending on the moment each individual tends to carry out the activities they do throughout the day such as eating, going to sleep and waking up, social life, working out, etc. There are morning, intermediate and evening types. Observation of contrast between each of them has shown that subjects with evening chronotype have more inclination to have disrupted feeding behaviours like meal skipping, nocturnal eating, addiction to food and increased calory intake in their diet in comparison to the rest (Vitale and Weydahl, 2017). As a result, further studies have confirmed that this attitude causes chrono disruption, affecting physiological pathways that can lead to metabolic issues, obesity and diabetes type 2 (Baron et al., 2017).

Given this premise, metabolic disruption can be palliated by eating at the right time, as it depends on the chronotype of each subject (Haraguchi et al., 2014).

4.3. INTRINSIC FACTORS

4.3.1. AGE

The older we get, the more scattered and less wide circadian acrophases are, resulting in a weaker circadian rhythm (Figure 11). Similarly, clock genes that participate in diseases related to the disruption of the circadian rhythm, are also present during aging, meaning that there's a relation between aging and circadian rhythm disruption (Cornelissen and Otsuka, 2017).

Researchers have pointed out the necessity of differentiating the characteristics of natural aging (senescence) from the diseases associated with aging (senility), although it's not easy since health is usually badly considered as the lack of disease (Tevy et al., 2013).

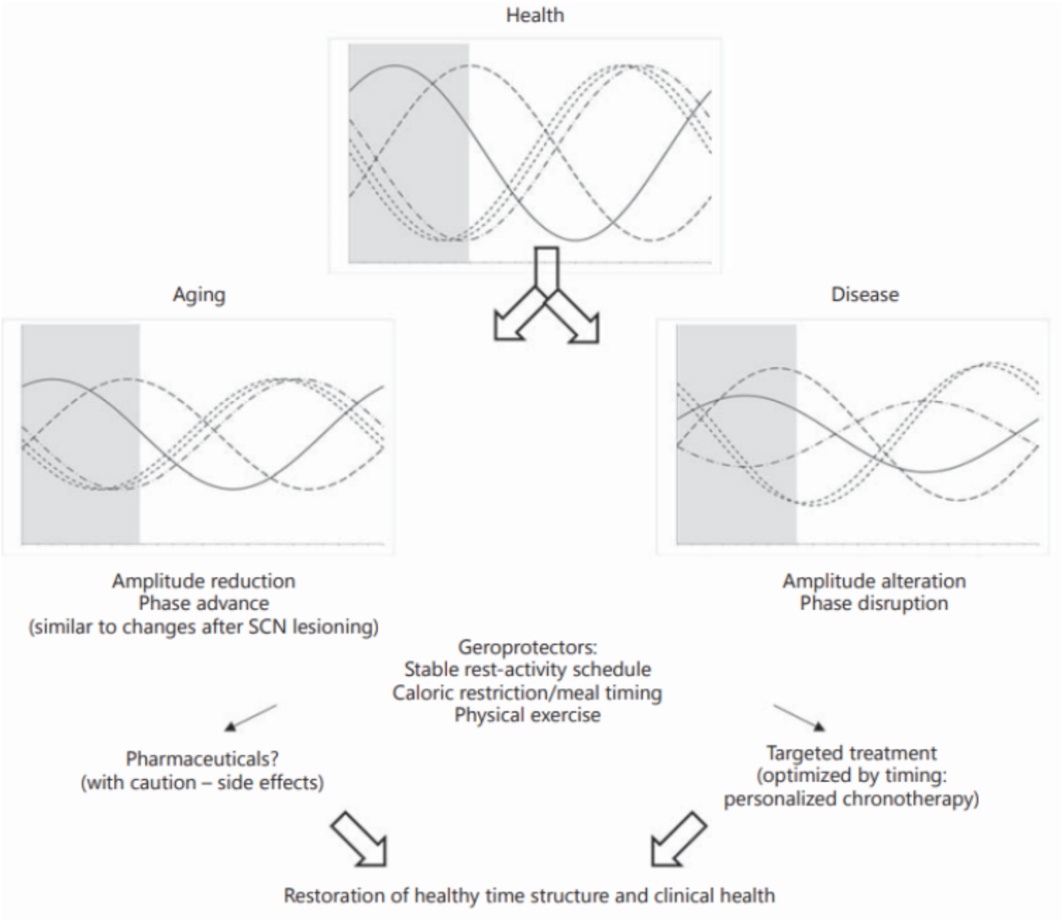


Figure 11. Diagram comparing the amplitude and phase of the circadian rhythms for each state: health, aging and disease. It also shows a series of coping geroprotector measures like stable rest-activity schedules, caloric restriction combined with meal timing and physical exercise. Also, in order to restore a healthy time structure and clinical health, it considers the use of pharmaceuticals with caution due to their side effects and a personalized chronotherapy (Cornelissen and Otsuka, 2017).

4.3.2. SEX

It's still unknown up to what extent biological sex and hormones intervene in the circadian rhythm (Krizo and Mintz, 2014). Differences between both sexes are quite dim, but there are some cases where the circadian clock response can differ like with drug addiction (Bobzean et al., 2014) or disease (Bailey and Silver, 2014).

4.4. IATROGENIC PHACTORS

4.4.1. INTERACTION WITH DRUGS

As explained previously, circadian rhythms have a great influence over many (if not all) biological processes and are key to the balance between health and disease, but they’re constantly adjusting to external cues and sometimes these can lead to chronodisruption.

For instance, drug addiction is one of the main problems among young adults as a big percentage aged between 18 and 25 consume substances of abuse such as alcohol, cannabis, hallucinogens, psychostimulants, opioids, etc. (United Nations Office on Drugs and Crime, 2020).

Moreover, it has been proved to interact with the circadian system, given that their use is determined by a circadian behaviour, being slowly modified as consumption and dependence grows (Figure 12) (Tamura et al., 2021). As a result of the circadian disruption caused by chronic drug use, coordination between the biological clock and the external signals ceases inducing health and well-being issues like fatigue, anhedonia and insomnia (Depoy et al., 2017).

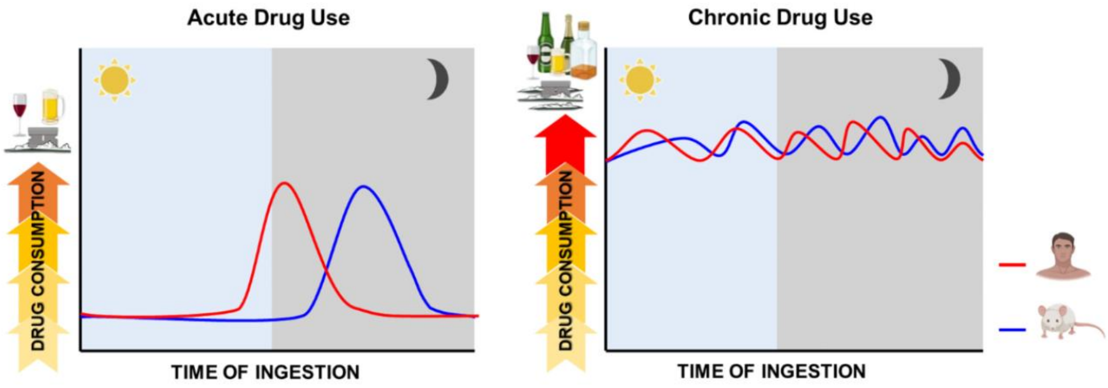


Figure 12. Representation of drug use timing in two different situations: acute use (on the left) and chronic use (on the right). In the first case, the most frequent moment of use is while in rest phase (beginning of the evening) for humans and while in active phase (dark) for mice. In the second case, there's no time nor rhythmic difference along the day and the consumption is higher (Tamura et al., 2021).

But not only drugs of abuse should be considered when studying the circadian rhythm. Applications of this knowledge to pharmacotherapy has opened a new dimension of personalized treatment, chronopharmacotherapy, with the aim of increasing the efficacy and decreasing the risks and side effects of the treatment (Nahmias and Androulakis, 2021).

5. CONCLUSION

All in all, there are many factors in place that directly influence negatively on the circadian rhythm, although there's still a lot of research needed to determine the importance of these in people's lives, specifically in modern society, where we are constantly surrounded by them and, without being aware, suffer long-term health consequences.

Therefore, human's lifestyle should strive to adjust to each individual's biological rhythm and not the other way around, in terms of sleep, feeding, working and social hours amongst other activities.

Also, manufactures should control electromagnetic radiation emissions from electric devices to protect their users and the industry must limit the quantity of emissions of chemical pollutants in order to preserve natural and healthy levels in the environment.

Finally, as mentioned above, individualized therapy should take into account everyone's chronotype to achieve a better treatment adjustment seeking more efficient and safer results.

6. REFERENCES

Aluru N, Krick KS, Mcdonald AM, Karchner SI. Developmental Exposure to PCB153 (2,2′,4,4′,5,5′-Hexachlorobiphenyl) Alters Circadian Rhythms and the Expression of Clock and Metabolic Genes. Toxicol Sci 2020;173: 41–52. https://doi.org/10.1093/toxsci/kfz217.

Bailey M, Silver R. Sex differences in circadian timing systems: Implications for disease. FIN. 2014;3: 11-139 https://doi.org/10.1016/j.yfrne.2013.11.003.

Baron KG, Reid KJ, Kim T, van Horn L, Attarian H, Wolfe L, et al. Circadian timing and alignment in healthy adults: Associations with BMI, body fat, caloric intake and physical activity. Int J Obes;41: 203-209 https://doi.org/10.1038/ijo.2016.194.

Bobzean SAM, DeNobrega AK, Perrotti LI. Sex differences in the neurobiology of drug addiction. Exp Neurol 2014;259: 64-74. https://doi.org/10.1016/j.expneurol.2014.01.022.

Chang AM, Aeschbach D, Duffy JF, Czeisler CA. Evening use of light-emitting eReaders negatively affects sleep, circadian timing, and next-morning alertness. Proc Natl Acad Sci U S A 2015;112: 1232-1237 https://doi.org/10.1073/pnas.1418490112.

Choi JY, Choe JR, Lee TH, Choi CY. Effects of bisphenol A and light conditions on the circadian rhythm of the goldfish Carassius auratus. Biol Rhythm Res 2018;49: 502-514 https://doi.org/10.1080/09291016.2017.1385977.

Cinzano P, Falchi F, Elvidge CD. The first World Atlas of the artificial night sky brightness. Mon Not R Astron Soc 2001;328: 689-707 https://doi.org/10.1046/j.1365-8711.2001.04882.x.

Contalbrigo L, Stelletta C, Falcioni L, Casella S, Piccione G, Soffritti M, et al. Effects of different electromagnetic fields on circadian rhythms of some haematochemical parameters in rats. Biomed Environ Sci 2009;22: 343-353 https://doi.org/10.1016/S0895-3988(09)60067-2.

Cornelissen G, Otsuka K. Chronobiology of Aging: A Mini-Review. Gerontology 2017;63: 118-128 https://doi.org/10.1159/000450945.

Danilenko K v., Cajochen C, Wirz-Justice A. Is sleep per se a zeitgeber in humans? J Biol Rhythm 2003;1: 170-178 https://doi.org/10.1177/0748730403251732.

Dasdag S, Sert C, Akdag Z, Batun S. Effects of extremely low frequency electromagnetic fields on hematologic and immunologic parameters in welders. Arch Med Res 2002;33: 29-32 https://doi.org/10.1016/S0188-4409(01)00337-X.

Depoy LM, McClung CA, Logan RW. Neural mechanisms of circadian regulation of natural and drug reward. Neural Plast 2017;2017 1-14 https://doi.org/10.1155/2017/5720842.

Dickmeis T. Glucocorticoids and the circadian clock. J Endocrinol 2009;200: 3-22 https://doi.org/10.1677/JOE-08-0415.

Diffey BL. An overview analysis of the time people spend outdoors. Brit J Dermatol 2011;164: 848-854 https://doi.org/10.1111/j.1365-2133.2010.10165.x.

Do MTH, Yau KW. Intrinsically photosensitive retinal ganglion cells. Physio Rev 2010;90: 1547-1581 https://doi.org/10.1152/physrev.00013.2010.

Faltermann S, Zucchi S, Kohler E, Blom JF, Pernthaler J, Fent K. Molecular effects of the cyanobacterial toxin cyanopeptolin (CP1020) occurring in algal blooms: Global transcriptome analysis in zebrafish embryos. Aquat Toxicol 2014;149: 33-39 https://doi.org/10.1016/j.aquatox.2014.01.018.

Garaulet M. ¿Qué es la cronobiología? Tu cuerpo, un reloj biológico. En: Planeta, editorial. Los relojes de tu vida. 4th edition. Barcelona: Paidós 2017. P 13-49.

Haraguchi A, Aoki N, Ohtsu T, Ikeda Y, Tahara Y, Shibata S. Controlling access time to a high-fat diet during the inactive period protects against obesity in mice. Chronobiol Int 2014;31: 935-944 https://doi.org/10.3109/07420528.2014.931413.

Haus E, Smolensky M. Biological clocks and shift work: Circadian dysregulation and potential long-term effects. Cancer Cause Control 2006;17: 489-500 https://doi.org/10.1007/s10552-005-9015-4.

Honma S. The mammalian circadian system: a hierarchical multi-oscillator structure for generating circadian rhythm. J Physiol Sci 2018;68: 207-219 https://doi.org/10.1007/s12576-018-0597-5.

Kelly C. 2020. Prescription Hope [Internet]. What is Circadian Rhythm? - Disorders, Symptoms, Health Effects; [consulted on February 25th, 2022]. Available in: https://prescriptionhope.com/blog-what-is-circadian-rhythm-disorders-symptoms-health-effects/.

Krizo JA, Mintz EM. Sex differences in behavioral circadian rhythms in laboratory rodents. Front Endocrinol 2014;5: 234 https://doi.org/10.3389/fendo.2014.00234.

Kumlin T, Heikkinen P, Laitinen JT, Juutilainen J. Exposure to a 50-Hz magnetic field induces a circadian rhythm in 6-hydroxymelatonin sulfate excretion in mice. J Radiat Res 2005;46: 313-318 https://doi.org/10.1269/jrr.46.313.

Kundi M, Mild KH, Hardell L, Mattsson MO. Mobile telephones and cancer - A review of epidemiological evidence. J Toxicol Env Health - Part B: Critical Reviews 2004;7: 351-384 https://doi.org/10.1080/10937400490486258.

Lange T, Dimitrov S, Born J. Effects of sleep and circadian rhythm on the human immune system. Ann N Y Acad Sci 2010;1193: 48-59 https://doi.org/10.1111/j.1749-6632.2009.05300.x.

Liang YQ, Huang GY, Zhen Z, Tian F, Hou L, Lin Z, et al. The effects of binary mixtures of estradiol and progesterone on transcriptional expression profiles of genes involved in hypothalamic-pituitary-gonadal axis and circadian rhythm signaling in embryonic zebrafish (Danio rerio). Ecotox Environl Safe 2019;174: 540-548 https://doi.org/10.1016/j.ecoenv.2019.03.021.

McEwen BS. Sleep deprivation as a neurobiologic and physiologic stressor: allostasis and allostatic load. Metabolism 2006;55: 20-23 https://doi.org/10.1016/j.metabol.2006.07.008.

Merrow M, Spoelstra K, Roenneberg T. The circadian cycle: Daily rhythms from behaviour to genes. Embo Rep 2005;6: 930-935 https://doi.org/10.1038/sj.embor.7400541.

Mignot E. Why we sleep: The temporal organization of recovery. Plos Biol 2008;6: 4 pages https://doi.org/10.1371/journal.pbio.0060106.

Moore RY. The suprachiasmatic nucleus and the circadian timing system. Prog Mol Biol Transl, vol. 119, 2013: 1-28 https://doi.org/10.1016/B978-0-12-396971-2.00001-4.

Nahmias Y, Androulakis IP. Circadian Effects of Drug Responses. Annu Rev Biomed Eng 2021;23: 203-224 https://doi.org/10.1146/annurev-bioeng-082120-034725.

Obot U. 2014. Every Day, Psychology [Internet]. amygdala – Every Day, Psychology; [consulted on April 12th, 2022]. Available in: https://profkraha.wordpress.com/tag/amygdala/.

Oggier DM, Weisbrod CJ, Stoller AM, Zenker AK, Fent K. Effects of diazepam on gene expression and link to physiological effects in different life stages in zebrafish danio rerio. Envir Sci Tech 2010;44: 7685-7691 https://doi.org/10.1021/es100980r.

Parrott JL, Metcalfe CD. Assessing the effects of the antidepressant venlafaxine to fathead minnows exposed to environmentally relevant concentrations over a full life cycle. Environ Pollut 2017;229: 403-411 https://doi.org/10.1016/j.envpol.2017.06.009.

Patowary K. 2019. Amusing Planet - Exploring Curiosities [Internet]. Linnaeus's Flower Clock: Keeping Time With Flowers; [consulted on March 16th, 2022]. Available in: https://www.amusingplanet.com/2019/07/linnaeuss-flower-clock-keeping-time.html?m=1

Podolin PL, Rollag MD, Brainard GC. The suppression of nocturnal pineal melatonin in the syrian hamster: Dose-response curves at 500 and 360 nm. Endocrinology 1987;121: 266-270 https://doi.org/10.1210/endo-121-1-266.

Poopal RK, Zhang J, Zhao R, Ramesh M, Ren Z. Biochemical and behavior effects induced by diheptyl phthalate (DHpP) and Diisodecyl phthalate (DIDP) exposed to zebrafish. Chemosphere 2020;252: page 126498 https://doi.org/10.1016/j.chemosphere.2020.126498.

Potter GDM, Skene DJ, Arendt J, Cade JE, Grant PJ, Hardie LJ. Circadian rhythm and sleep disruption: Causes, metabolic consequences, and countermeasures. Endoc Rev 2016;37: 584-608 https://doi.org/10.1210/er.2016-1083.

Qiao Q, le Manach S, Huet H, Duvernois-Berthet E, Chaouch S, Duval C, et al. An integrated omic analysis of hepatic alteration in medaka fish chronically exposed to cyanotoxins with possible mechanisms of reproductive toxicity. Environm Pollut 2016;219: 119-131 https://doi.org/10.1016/j.envpol.2016.10.029.

Rabearivony A, Li H, Zhang S, Chen S, An X, Liu C. Housing temperature affects the circadian rhythm of hepatic metabolism and clock genes. J Endocrinol 2020;247: 183-195 https://doi.org/10.1530/JOE-20-0100.

Refinetti R. Circadian rhythmicity of body temperature and metabolism. Temperature 2020;7: 321-362 https://doi.org/10.1080/23328940.2020.1743605.

Rosenwasser AM, Turek FW. Physiology of the Mammalian Circadian System. Principles and Practice of Sleep Medicine: Fifth Edition, Elsevier Inc.; 2010, p. 390–401. https://doi.org/10.1016/B978-1-4160-6645-3.00034-7.

Rybnikova NA, Haim A, Portnov BA. Does artificial light-at-night exposure contribute to the worldwide obesity pandemic? Int J Obesity 2016;40: 815-823 https://doi.org/10.1038/ijo.2015.255.

Spieler RE, Russo AC, Weber DN. Waterborne lead affects circadian variations of brain neurotransmitters in fathead minnows. B Environ Contam Toxi 1995;55: 412-418 https://doi.org/10.1007/BF00206680.

Stelletta C, de Nardo P, Santin F, Basso G, Michielotto B, Piccione G, et al. Effects of exposure to extremely low frequency electro-magnetic fields on circadian rhythms and distribution of some leukocyte differentiation antigens in dairy cows. Biomed Environ Sci 2007;20: 164-170

Tamura EK, Oliveira-Silva KS, Ferreira-Moraes FA, Marinho EAV, Guerrero-Vargas NN. Circadian rhythms and substance use disorders: A bidirectional relationship. Pharmacol Biochem Be 2021;20: 173105 https://doi.org/10.1016/j.pbb.2021.173105.

Tevy MF, Giebultowicz J, Pincus Z, Mazzoccoli G, Vinciguerra M. Aging signaling pathways and circadian clock-dependent metabolic derangements. Trends Endocrin Met 2013;24: 229-237 https://doi.org/10.1016/j.tem.2012.12.002.

Theodoratou E, Tzoulaki I, Zgaga L, Ioannidis JPA. Vitamin D and multiple health outcomes: Umbrella review of systematic reviews and meta-analyses of observational studies and randomised trials. BMJ (Online) 2014;348: g2035 https://doi.org/10.1136/bmj.g2035.

United Nations Office on Drugs and Crime. The world drug report 2020. Booklet 2 Drug use and health consequences. 2020.

Vicario-Parés U, Lacave JM, Reip P, Cajaraville MP, Orbea A. Cellular and molecular responses of adult zebrafish after exposure to CuO nanoparticles or ionic copper. Ecotoxicology 2018;27: 89-101 https://doi.org/10.1007/s10646-017-1873-5.

Vitale JA, Weydahl A. Chronotype, Physical Activity, and Sport Performance: A Systematic Review. Sports Med 2017;47 1859-1868 https://doi.org/10.1007/s40279-017-0741-z.

Wright KP, McHill AW, Birks BR, Griffin BR, Rusterholz T, Chinoy ED. Entrainment of the human circadian clock to the natural light-dark cycle. Curr Biol 2013;23: 1554-1558 https://doi.org/10.1016/j.cub.2013.06.039.

Xiao B, Cui LQ, Ding C, Wang H. Effects of Lithium and 2,4-Dichlorophenol on Zebrafish: Circadian Rhythm Disorder and Molecular Effects. Zebrafish 2017;14: 209-215 https://doi.org/10.1089/zeb.2016.1389.

Yang M, Ren Baigang, Qiao L, Ren Baixiang, Hu Y, Zhao R, et al. Behavior responses of zebrafish (Danio rerio) to aquatic environmental stresses in the characteristic of circadian rhythms. Chemosphere 2018;210: 129-138 https://doi.org/10.1016/j.chemosphere.2018.07.018.

Yang Y, Dong F, Liu X, Xu J, Wu X, Zheng Y. Dysregulation of circadian rhythm in zebrafish (Danio rerio) by thifluzamide: Involvement of positive and negative regulators. Chemosphere 2019a;235: 280-287 https://doi.org/10.1016/j.chemosphere.2019.06.153.

Yang Y, Dong F, Liu X, Xu J, Wu X, Zheng Y. Flutolanil affects circadian rhythm in zebrafish (Danio rerio)by disrupting the positive regulators. Chemosphere 2019b;228: 649-655 https://doi.org/10.1016/j.chemosphere.2019.04.207.

Zhang H, Chen ZF, Qi Z, Yan SC, Wei WW, Liu G, et al. Analysis of transcriptional response in zebrafish eleutheroembryos exposed to climbazole: Signaling pathways and potential biomarkers. Environ Toxicol Chem 2019;38: 794-805 https://doi.org/10.1002/etc.4355.

Zhao Y, Zhang K, Fent K. Regulation of zebrafish (Danio rerio) locomotor behavior and circadian rhythm network by environmental steroid hormones. Environ Pollut 2018;232: 422-429 https://doi.org/10.1016/j.envpol.2017.09.057.

Zheng X, Zhang K, Zhao Y, Fent K. Environmental chemicals affect circadian rhythms: An underexplored effect influencing health and fitness in animals and humans. Environ Int 2021;149: 106-159 https://doi.org/10.1016/j.envint.2020.106159.

Zucchi S, Mirbahai L, Castiglioni S, Fent K. Transcriptional and physiological responses induced by binary mixtures of drospirenone and progesterone in zebrafish (Danio rerio). Envir Sci Tech 2014;48: 3523-3531 https://doi.org/10.1021/es405584f.