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EPIGENETICS AND PINEAL GLAND: EFFECTS OF EPIGENETICS ON MENTAL HEALTH

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Abstract: Advances in epigenetic studies on how environmental stimuli interact in the specific activation of genes reveal a new importance in the study of the pineal gland, shifting the focus from the circadian cycle and positioning itself in the actions of melatonin on mental health, through the interaction between epigenetics and the pineal gland. In this work, we present the most recent promising studies on the subject, in order to unravel the interaction of epigenetics with the pineal gland. An integrative review was carried out through a bibliographic survey of articles and books. It was identified that most of the articles and books separately address epigenetics, the pineal gland, and mental health, associating two of these terms in some cases. The interaction of epigenetics in the pineal gland acting on mental health needs to be analyzed in depth based on the studies undertaken since it is already known that melatonin plays a fundamental role in treatments for depression and other health conditions.

Keywords: Melatonin. Serotonin. Circadian rhythms. Well-being. Depression.

INTRODUCTION

Mental health has been a topic of discussion worldwide for several years. However, following the events of the technological boom from the first decade of the 21st century and the COVID-19 pandemic, a number of articles have been written presenting the theme, and some specific terms about mental health disorders have been created, such as "Phantom Touch Syndrome," "Nomophobia," "Coronaphobia," and "New Normal." These are examples of how the environment has impacted the mental health state of the population worldwide.

According to the Ministry of Health, strategies and assistance measures to be adopted in Brazil should cover people with "needs related to mental disorders such as depression, anxiety, schizophrenia, bipolar affective disorder, obsessive-compulsive disorder [...]" (HEALTH..., 2022, p. 1). Data from Fiocruz indicate that before the COVID-19 pandemic in 2019, there were 7.8% cases of depressive and anxiety disorders in the world population. In 2020, the year of the pandemic outbreak, cases of depressive and anxiety disorders reached 9,8% - an increase of over 25% (FUNDAÇÃO OSWALDO CRUZ, 2022).

The pineal gland and epigenetics have been addressed since the late 20th century with the publication of several articles after the advent of emerging technologies and the discussion of concepts that could bring these new studies to light. The pineal gland was previously treated as an irrelevant organ and a remnant of human evolution. Epigenetics, on the other hand, began to be analyzed after the interference of the environment on DNA structure and specific gene activation at the molecular level became more noticeable.

The pineal gland is considered the main producer of melatonin, and according to Karamitri and Jockers (2019, cited in PROCHNOW et al., 2022, p. 410), melatonin "is known for its regulatory role in the circadian cycle and has been widely studied as a possible adjunct in the treatment of obesity and other associated comorbidities."

According to Song (2019), epigenetics can be a solution to understanding the functioning of the pineal gland. Recent studies demonstrate that the function of the pineal gland can be epigenetically regulated through the use of valproic acid (VPA), which acts positively on the expression of the melatonin receptor in the brain.

Taking the analysis of articles and books as a starting point, this work aims to reflect on the capabilities of this tiny organ called the Pineal Gland, which is of great importance in mental health, and the possible effects epigenetics may cause on this gland's functioning that could influence mental health.

PINEAL GLAND

According to Graaff and Marshall (2003), the pineal gland is a small conical gland attached to the roof of the third ventricle and encapsulated by the meninges that also protect the brain, with a size of 5 to 8mm in height and 9mm in width in children and decreases from the age of 7. In adults, the gland aspect resembles a thick fibrous tissue filament, with a specialized parenchymal tissue and neuroglial cells, and is highly innervated by the sympathetic division of the autonomic nervous system.

Ilahi, Beriwal, and Ilahi (2022) describe that studies in rodents demonstrate that there are other functions for the pineal gland, such as in chemical metabolism, where it can influence the actions of some drugs, such as antidepressants and cocaine. It was also identified that when the pineal gland was removed in rodents, there was an increase in the production of both the Follicle Stimulating Hormone (FSH) and Luteinizing Hormone (LH).

Barrett et al. (2014, p. 280) affirm that "in infants, the pineal gland is large and the cells tend to be arranged in alveoli. It begins to involute before puberty, and small concretions of calcium phosphate and carbonate (pineal sand) appear in the tissue".

Lucchetti et al. (2013) provide a historical context of the endocrine function of the pineal gland, although Huebner was the first to describe this function in 1898 by reporting a case of a boy with pinealoma and precocious puberty. However, only in 1943, Bergmann's study on mammals suggested that the pineal gland could have a role in regulating the hypothalamic function.

As explained by Axelrod (1974 apud NETO; CASTRO, 2008), the pineal gland synthesizes melatonin from serotonin. Neto and Castro (2008) describe that melatonin secretion only occurs at night, beginning around 2 hours before the usual bedtime, with peaks occurring between 3 and 4 a.m., in accordance with the individual's chronotype.

Graaff and Marshall (2003) describe that melatonin has a circadian rhythm linked to daily and seasonal changes in light exposure. The cycle of melatonin stimulation is shown in Figure 1 and described below by the authors.

> The secretion of melatonin by the pineal gland is stimulated by sympathetic axons that originate in the superior cervical ganglion. The activity of these neurons is regulated by the cyclic activity of the suprachiasmatic nucleus of the hypothalamus, which describes a circadian rhythm that is driven in cycles of light/dark by neurons in the retina (Graaff; Marshall, 2003, p. 475).

It has been claimed by Barrett et al. (2014) that the circadian rhythm has a synchronization process dependent on the suprachiasmatic nuclei (SCN), which are responsible for receiving information about the light/dark cycle from vision through the retinohypothalamic tract, which will synchronize circadian rhythmicity, including the sleep-wake cycle and melatonin secretion.

The duration of the circadian rhythm is on average 6 to 8 hours of sleep for 16 to 18 hours of wakefulness, completing a 24-hour cycle. The synchronization of this cycle is mainly related to the alternation between light and dark, but also has interference from social interactions, feeding cycles, physical exercise, among others (DUARTE, 2018).

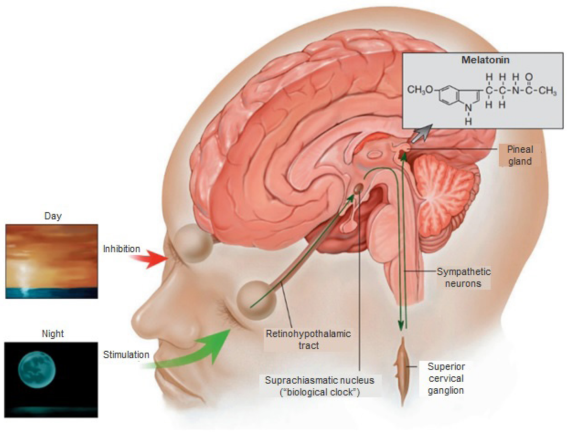


Figure 1: Melatonin stimulation and inhibition process. Source: Graaff and Marshall (2003).

The production of melatonin follows a cycle based on the absence of light and is commonly referred to as the sleep hormone. Figure 2 shows that melatonin production increases around 8 pm, reaching its peak production at around 3-4 am, as previously mentioned. Its production rapidly decreases in the early morning until it reaches the daily production level.

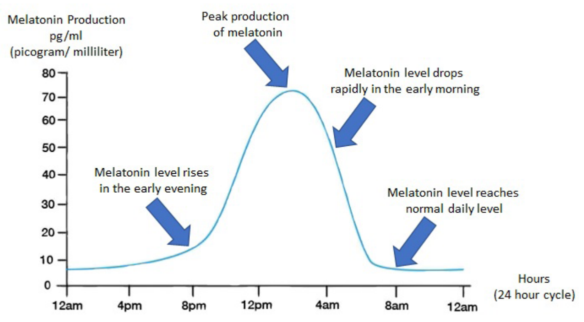


Figure 2: Melatonin production levels at night. Adapted SLEEP (2018).

It is evident that light is an environmental factor of extreme importance in melatonin production and absorption. During the dark period, also known as the dark phase, the SCN (suprachiasmatic nucleus) is inactive, and the pineal gland is activated for melatonin production. At sunrise, the SCN becomes active and has an inhibitory action on the pineal gland. It is important to note that light exposure during the dark phase will inhibit melatonin production. For instance, exposure to an environment with illuminance between 50 and 300 lux, which is equivalent to approximately one LED lamp between 2 and 5W, will inhibit melatonin production during exposure to that light intensity. Exposure to an environment with illumination between 2000 and 2500 lux, which is equivalent to approximately two LED lamps of 10W, for approximately two hours, will be sufficient to completely inhibit the pineal gland in humans during the cycle. Repeated exposures to light may lead to a delay in melatonin release, a process referred to as "phase delay," as shown in Figure 3 (NETO; CASTRO, 2008).

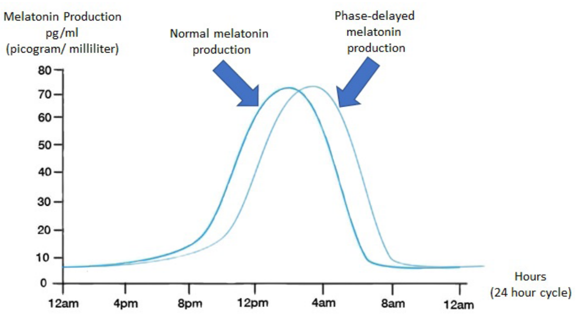


Figure 3: Phase delay. Adapted SLEEP (2018).

It has been observed that individuals with "phase delay" tend to have a tendency to sleep later and, consequently, have difficulty getting up early. According to Goweda et al (2020 apud SILVEIRA; VÉRAS, 2022), exposure to screens during the use of smartphones and television is related to the development of sleep disorders. The study by Kaya, Dastan, and Durar (2020 apud SILVEIRA; VÉRAS, 2022) shows a negative correlation between the duration of use of these devices and the circadian rhythm. According to Dutra da Silva et al (2021 apud SILVEIRA; VÉRAS, 2022), approximately 55% of the students in their research at a university in the state of Goiás presented excessive daytime sleepiness

(EDS) or hypersomnia, which can result in a decrease in the ability to memorize and an inability to stay awake, leading to unintentional sleep lapses.

Staying in brightly-lit environments until late hours, as well as using devices with electronic screens, can induce phase delay and EDS, thus impairing the individual's quality of life, as they will constantly feel sleepy during wakefulness.

EPIGENETICS

According to Jablonka and Lamb (2002), the concept of epigenetics is not new. It was first defined by Conrad Waddington in the 1940s, based on the Aristotelian theory of epigenesis, where "epi" means "upon" in the sense of studying what was above traditional genetics. For Waddington, a simple mutated gene and its phenotypic effects are not based on a simple relationship, but rather, the mutation of a gene influences other genes, and this interaction composes a new phenotype.

The definition of epigenetic is "relating to the non-genetic causes of a phenotype" (SNUSTAD; SIMMONS, 2017, p. 544), meaning that epigenetic causes are non-genetic causes that alter a phenotype without altering its genotype. It is understood that epigenetics is based on alterations associated with active or repressed chromatin and genes, and is a reversible process. However, in complex epigenetic processes, such as DNA methylation, modifications, and variations of histones, these alterations can be more resistant to possible changes, becoming more stable and potentially long-lasting, capable of being transmitted to subsequent generations without modifying the DNA (MCINNES; WILLARD; NUSSBAUM, 2016).

In DNA methylation, there is a modification of cytosine bases by methylation of the 5-carbon of the pyrimidine ring. DNA methylation is considered a stable epigenetic mark and, as a consequence, can be transmitted in cell division and is frequently observed in cancer cells. Histone modifications involve modifications such as methylation, phosphorylation, or acetylation in one of the various main types of histones (H2A, H2B, H3, and H4), causing specific amino acid residues in the histone tails, influencing chromatin compaction, thus altering gene expression. Histone variants are variations that occur in completely different gene products and their amino acid sequences, which can mark specific regions or loci in the genome with highly specialized functions (MCINNES; WILLARD; NUSSBAUM, 2016). In Figure 4, we can see an example of cytosine methylation.

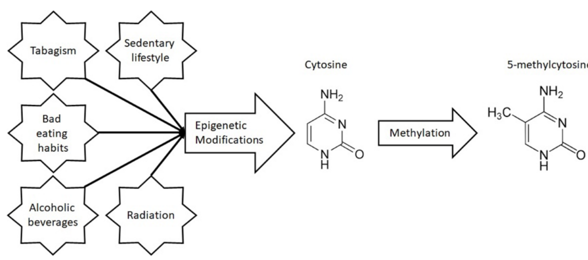


Figure 4: Schematic representation of cytosine methylation.

According to Francis (2015), the external environment in which a person is inserted can cause changes in genes, although this is not a direct effect, and a different reaction may occur for each type of cell. In studies with descendants of people who lived through the atrocities of World War II, such as the food embargo caused by the Nazi regime in the Netherlands, it was possible to verify the damage caused to the embryos of pregnant women (FRANCIS, 2017). Furthermore, according to Francis (2017), records analyzed in the 1970s showed that those who were between the second and third month of gestation during exposure to famine experienced problems with obesity in their adult life, and a subsequent study also concluded that there was a "significant increase in the risk of developing schizophrenia among those who had been exposed to Dutch famine during gestation" (FRANCIS, 2017, p. 18).

According to Fantappie (2013), several studies have already proven that epigenetic inheritance, in which the experiences lived by parents such as food, mistreatment, and hormonal treatments, can be transmitted to future generations. Francis (2017) describes that such environmental effects that alter epigenetic inheritance can be transmitted to future generations. For this, Francis coined the term "grandmother effect."

MENTAL HEALTH

Since its constitution, the World Health Organization (WHO) has included and defined mental well-being as "a state of complete physical, mental, and social well-being and not merely the absence of disease or infirmity" (WORLD HEALTH ORGANIZATION et al., 2004, p. 2).

Today, in the face of daily pressures experienced mainly by adolescents and adults, it is not easy to be in a "state of complete physical, mental, and social well-being", and often a clinical approach is required to provide individuals with the necessary conditions to achieve this highly coveted state.

Identifying a mental disorder is elaborate and complex since several aspects are described to locate it in the DSM-5 (which stands for Diagnostic and Statistical Manual of Mental Disorders). These aspects require the following elements:

A mental disorder is a syndrome characterized by clinically significant disturbance in an individual's cognition, emotional regulation, or behavior that reflects a dysfunction in the psychological, biological, or developmental processes underlying mental functioning. Mental disorders are often associated with significant suffering or impairment that affect social, occupational, or other important activities. A culturally expected or approved response to a common stressor or loss, such as the death of a loved one, does not constitute a mental disorder. Social deviance or conflicts that are primarily between the individual and society are not mental disorders unless the deviance or conflict is a symptom of a dysfunction in the individual, as described (AMERICAN PSYCHIATRIC ASSOCIATION, 2015, p. 96).

Among the various types specified in the DSM-5, some of the more well-known ones include depression, bipolar affective disorder, schizophrenia, dementia, among others (AMERICAN PSYCHIATRIC ASSOCIATION, 2015, p. 96).

Silva et al. (2022) describe that patients with bipolar affective disorder (BAD) have an inadequate secretion of melatonin. The authors describe that the mood state and depression in patients with BAD are linked to alterations in the circadian rhythm cycle.

Silva and Freitas (2021, p. 64) highlight in their studies that "mental disorders, diseases, and behaviors are influenced and inherited by epigenetic mechanisms."

According to Junior, Neris, and Oliveira (2018), epigenetics is an important field of study for psychology, as it demonstrates the link between genetic factors and the environment. Thus, epigenetics leads to an analysis of mental disorders not only by predetermined genetic factors but also by expanding the process of analyzing the formation of the individual throughout their history.

Recently, the COVID-19 pandemic has caused people to change their usual environments and become reclusive due to the lockdowns required by various governments to contain the SARS-CoV-2 virus, resulting in a 25% increase in cases of anxiety and depression, according to a study by PAHO. Multiple factors determined these cases depending on the environment in which the individual finds themselves, for example, healthcare professionals due to the exhaustion caused by long working hours, people who live alone who needed to work from home, people who lost loved ones to the disease; all these factors triggered anxiety, depression, and even suicide (ORGANIZAÇÃO PAN-AMERICANA DE SAÚDE, 2022).

In the studies by Souza and Lazzaretti (2021, p. 6), "it was found that depression is interrelated with melatonin regarding alterations in the circadian cycle, and specifically depressive symptoms and associated comorbidities." Thus, the use of melatonin analog drugs, such as agomelatine, is effective for the treatment of depression (SOUZA; LAZZARETTI, 2021).

According to Lucchetti et al. (2013), in the view corroborated by Spiritist doctrine in 1940, there is a strong relationship between the pineal gland and the individual's mental health, described as "[...] the gland of mental life [...] that presides over the nervous phenomena of emotivity" Xavier (1945 apud LUCCHETTI et al., 2013). For the authors, such facts presented a "remote and futuristic notion for the 1940s", a time when the book Missionaries of the Light by Francisco Cândido Xavier was written (LUCCHETTI et al, 2013, p. 5).

Lucchetti et al (2013) draw a conclusion about the involvement of the pineal gland in mental health:

> The analyzed studies suggest that the pineal gland plays a significant role in individuals' mental lives and simultaneously point out that this organ is "the gland of mental life." Current evidence reveals the existing relationship between the pineal gland and mental life, including the role of melatonin receptor agonists in the treatment of depression. However, the role of the pineal gland in individuals' mental lives is not yet completely elucidated.

According to Korkmaz and Reiter (2008), enzymes that act on DNA, called DNA methyltransferases (DNMTs), have a determining role in epigenetic regulation, since they promote the methylation of cytosine. Melatonin and its metabolites have a structure similar to DNMTs and could hypothetically inhibit them both by masking target sequences and by blocking the enzyme's active site since melatonin first eliminates these toxic compounds and then is converted into active metabolites, as shown in Figure 5.

Korkmaz and Reiter (2008) emphasize that epigenetic modifications are also responsible for various diseases other than cancer and that the epigenetic effectiveness of melatonin should be investigated by the readers of the article, not only in DNMTs.

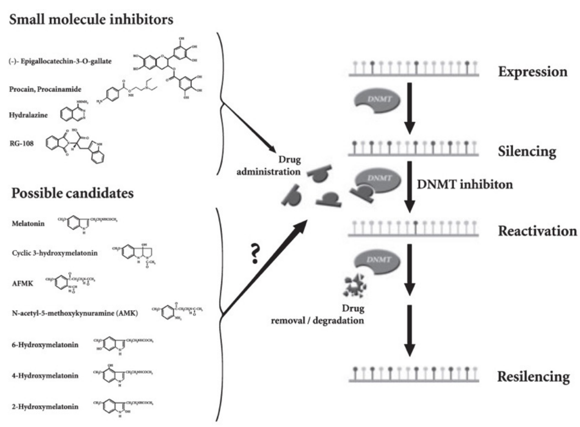


Figure 5: Use of melatonin as a DNMT inhibitor. Source: Korkmaz and Reiter (2008).

Hardeland (2014) considers that melatonin's actions through epigenetic mechanisms modulate the expression of melatonin target cells' receptors. The author describes that in C6 glioma cells, experiments using valproic acid (a medication indicated for the treatment of epilepsy and bipolar disorder) resulted in changes in the expression of the MTNR1A melatonin receptor gene (which encodes the melatonin 1 receptor) and were accompanied by changes in the mRNA levels of the methyl-CpG-binding protein 2 (MeCP2) and histone deacetylases (HDAC1, 2, and 3). These changes indicate that both DNA methylation patterns and chromatin remodeling via histone deacetylation may be associated with changes in MT1 expression.

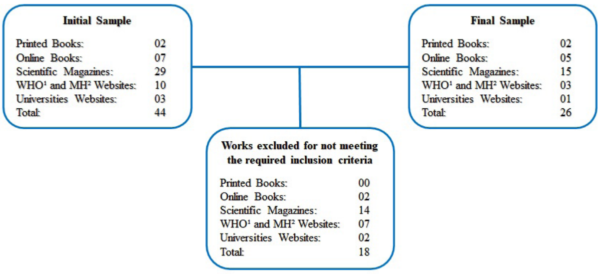
Thus, the interaction between the pineal gland and the effects of epigenetics on well-being is clear. Epigenetics can bring about advances still unknown to researchers and scientists, and therefore, the need to seek new content and disseminate it is of utmost importance so that new ideas and research emerge, bringing new achievements to science.

MATERIALS AND METHODS

This study is an integrative review that follows the methodological procedures outlined by Mendes et al. (2008). The purpose of this method is to synthesize and incorporate the best and most recent evidence and research findings on a particular topic or issue in a systematic, organized, and comprehensive manner.

To locate the materials for this study, the following databases were accessed: Google Scholar, Scielo, PubMed, Minha Biblioteca platform, NCBI (National Center for Biotechnology Information), and Wiley Online Library.

The selection criteria were based on the content related to epigenetics, the pineal gland, and mental health, using the following keywords: epigenetics, pineal gland, epiphysis, melatonin, mental health, and well-being. Articles and books in any language, published between 2000 and 2022, were considered. After a selective and objective reading, articles and books were chosen, taking into account the year of publication, place of publication, as well as the results and conclusions. Based on these criteria, 26 materials were selected, as presented in Figure 6 with the aforementioned indicators.



WHO[1] Websites: World Health Organization websites;
MH[2] Websites: Brazilian Ministry of Health websites.

Figure 6: Flowchart for article selection focusing on the topic.

RESULTS AND DISCUSSION

In the selected materials, the separate treatment of epigenetics, the pineal gland, and mental health was observed. In few materials, the terms epigenetics and the pineal gland were present at the same time, and when they were, they were focused on the role of melatonin in the synchronization of circadian rhythm, as observed in the articles by Barrett et al (2014), Graaff and Marshall (2003), Jablonka and Lamb (2002), Lucchetti et al (2013), Mcinnes, Willard, and Nussbaum (2016), Neto and Castro (2008), Silveira and Véras (2022), Snustad and Simmons (2017).

Among the selected materials, the term epigenetics was present in 26% of the titles, mental health in 21%, and the pineal gland in 5%, showing the little direct content of the pineal gland in publications focused on mental health. However, the pineal gland is not less valued by researchers, as the academic Journal of Pineal Research exists, which deals with research on the pineal gland and its hormonal products, with emphasis on melatonin in all vertebrate species. This journal did not present specific articles on the topic in question, placing more emphasis on the need for more studies on this topic.

CONCLUSION

The materials presented here complement each other, converging towards an understanding of the capacity of the pineal gland to undergo direct influences from epigenetics, and thus, having implications for mental health.

Epigenetics brings questions and answers to many inquiries, mainly demystifying the notion that genetic inheritance is purely based on the genetic sequence and that there is nothing to be done about it. At the same time, we see the mental health of the population reaching levels of illness never before seen, with the COVID-19 pandemic playing a role in this. Between epigenetics and mental health, the pineal gland emerges as a small point, well-protected by the human skull, with its poorly understood functions and considered insignificant by a large part of researchers, who have labeled it as a gland of prehistoric residues and underdeveloped after human evolution for a long time.

Current science and medicine have advanced and can now delve deeper into their research. It is up to them to shed the necessary light for the correct understanding of the pineal gland and, together with epigenetics, provide new treatments for mental health. The issue to be addressed here is no longer whether it will be possible, but when it will be possible.

With this study, it is understood that new research needs to be conducted soon, with a central focus on the topic discussed here, as it can bring scientific evidence that a treatment involving epigenetics and the pineal gland can bring good results for human mental health.

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