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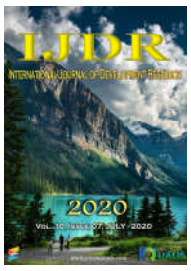

RESEARCH ARTICLE OPEN ACCESS

USE OF MELATONIN AS A LOW COST TREATMENT IN FIBROMYALGIA

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ABSTRACT

Melatonin is a hormone produced by the pineal gland, synthesized from tryptophan and derived from serotonin by replacing the hydroxyl group with methoxy, after enzymatic transformations. It is released in the absence of light, signaling the existence and alternation between light / dark and the seasons. This work aims to understand the role and function of melatonin as an antinociceptive agent. The methodology used consisted of research in works published on Scielo, Bireme and Periodicals CAPES websites. Among the many effects of melatonin, antinociceptive action is included, since it produces a marked anti-inflammatory effect in peripheral sites, inhibiting the release of pro-inflammatory cytokines. Fibromyalgia is defined as a disease that mainly affects the muscles, and the fibromyalgia syndrome is also classified as a type of extra-articular, non-infectious rheumatic disorder that affects the soft parts of the body (muscles, ligaments and tendons) and non-joints. It is a complex disease that can be acquired by genetic causes or by stress. According to the World Health Organization - WHO, the disease affects 30% of the world population, and fibromyalgia syndrome affects about 2% to 4% of the adult population in accidental countries, with women 5 to 9 times more affected than men. The use of melatonin in the treatment of fibromyalgia has been shown to act as an antinociceptive, decreasing pain and symptoms of depression, however studies on this topic are still scarce.

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INTRODUCTION

Melatonin is a remarkable molecule, with several physiological functions and some of its effects are measured by receptors, while others depend directly and indirectly on free radicals. Among the many effects of melatonin, antinociceptive action is included, that is, in reducing pain. Opioid neurotransmission has been shown to be involved in melatonin analgesia. Results using melatonin receptor antagonists support the participation of its receptors in analgesia (SRINIVAN *et al*., 2010). Melatonin produces a marked anti-inflammatory effect in peripheral sites, inhibiting the release of pro-inflammatory cytokines (CUZZPCREA, 1997; 2001). The pineal gland produces melatonin, a hormone synthesized from tryptophan and derived from serotonin by replacing the hydroxyl group with methoxy, after enzymatic transformations (HOHL *et al*., 2016). In mammals, the pineal gland is primarily responsible for the transduction of the environmental photoperiod into endocrine hormonal signaling. Melatonin is then released during the dark, signaling the existence and duration of that period, that is, it signals the alternation between light / dark and between the seasons. The production of melatonin by the pineal increases about 60 to 100 times during the night, being considered the hormonal expression of the biological clock. This system makes it possible to anticipate internal biological functions to cyclical environmental events, with adaptation to variations in these external oscillatory stimuli controlled by signaling hormones such as melatonin. In some pathological situations, pineal function is suppressed and the organism is no longer informed of the existence of the dark. Animal studies suggest that both psychological and physical stress can produce dysfunctions in this axis (MORGAN *et al*., 1994; YU *et al*., 2000). The possible mechanisms by which melatonin can interfere with inflammatory and algogenic processes are: inhibition of nitric oxide production and reduction of the expression of the enzyme nitric oxide synthase at the transitional level; activation of the NF - KB transcription power; reduction of the

expression of the nitric oxide synthase enzyme at the transferional level; reduced levels of prostaglandins and expression of cribo-oxignil-2; reduction of recruitment of polymorphonuclear cells in the inflamed site (CUZZOCREA, 2010). Also, the analgesic effect of melatonin is probably specific to M1 and M2 types. Despite the importance of melatonin in antinociceptive action, reducing pain, studies on this topic are scarce. Cetera *et al*. (2000) carried out work to determine the possible effect of treatment with melatonin on sleep symptoms, fatigue and pain in patients with fibromyalgia. Press *et al*. (1998) evaluated the levels of melatonin in urine measured by 6-sulfatoxymelatonin (aMT6s) in patients with fibromyalgia. Pineal (2011) makes a study to review the analgesic effect of melatonin. All conclude the need for further studies. Therefore, it is necessary that more studies be developed trying to evaluate the antinociceptive action of melatonin, especially in fibromyalgia. In this sense, this work aims to understand, through an in-depth review, the role and function of melatonin as an antinociceptive agent, aiming to contribute to the use of melatonin as a low-cost medication in cases of fibromyalgia in patients in Brazil. Furthermore, to emphasize specifically to investigate the diagnoses of fibromyalgia, to investigate the antinociceptive action of melatonin and the use of melatonin to decrease pain in fibromyalgia. It is hoped that the results of this research may represent an advance in the diagnosis of fibromyalgia, in addition to effectively helping health professionals to prevent or minimize the harmful consequences of chronic pain. However, further studies are needed to determine the mechanisms by which exogenous melatonin modulates nociceptive circuits.

MATERIAL AND METHODS

A literature review was carried out, research on the subject of this study was carried out: melatonin, pain and fibromyalgia on specialized sites such as Scielo, Google Scholar, Bireme and CAPES Journals, and other works that address the topic addressed here, both in Portuguese as in English. Priority was given to articles published from 1990 to the present date, except in cases of classic works of recognized academic value. The information obtained was written in a systematic way, aiming to provide precise and clarifying information, in the form of a review monograph, which can be sent to a reputable journal in human physiology. As a result of the research carried out, it was found that melatonin (N-acetyl-5-methoxytryptamine) is a hormone synthesized by the pineal gland found in vertebrates. It was discovered by dermatologist Aaron Lerner, in 1958, who adopted this name due to its ability to contract melanocytes from frog melanocytes. However, it was only in the 1960s that the relationship between ambient light and the metabolic activity of the pineal gland was established, showing the daily rhythm of serotonin and melatonin. The main function of the pineal gland is the rhythmic production of melatonin. It is a neuroendocrine gland and suprachiasmatic nuclei play an essential role in the daily variation of melatonin production, generating the rhythm and spreading the light response detected by the retina (KENNAWAY and WRIGHT, 2002). Melatonin is synthesized from serotonin in the following sequence of reactions: conversion of tryptophan to serotonin; conversion of serotonin to Nacetylserotonin (mediated by arylalkylamine-Nacetyltransferase); conversion of N-13 acetylserotonin to melatonin (mediated by hydroxy-indole-O-methyltransferase) (CLAUSTRAT *et al*., 2015). It is secreted in a rhythmic manner in the circulation and in the various bodily fluids, informing the organism if it is day or night abroad and also its nocturnal plasma profile, that is, its duration, indicates the season (REITER, 1980). Therefore, melatonin is an essential signal both for synchronizing daily rhythms and seasonal phenomena. The production of melatonin occurs exclusively at night, in general it starts about 2 hours before the usual bedtime and reaches maximum plasma levels between 03:00 and 04:00 hours (CLAUSTRAT *et al*, 2015), but it can vary from according to the pace of each individual. Then, the secreted melatonin is distributed to several body tissues, not being stored (ROSS *et al*., 2002). It presents high solubility in lipids, which facilitates its passage through cell membranes, crossing, including the blood-brain barrier. In vertebrate organisms, it can be produced in other structures besides the pineal gland or comparable brain extrusions, such as the retina or in the reptiles in the parietal organs, but also in other organs and cells, including the Harderian gland, the membranous cochlea, the mononuclear leukocytes , the skin, and the gastrointestinal tract, which contains several hundred times more than the melatonin produced in the pineal gland (HARDELAND, 2005). However, these places of production of extra pineal melatonin contribute little, or only by means of specific stimuli, for the circulation of melatonin (HARDELAND, 2005). In this study, it was found that melatonin has a possible role in the early stages and development of degenerative diseases of age. The production of melatonin undergoes a gradual decline during aging. The rate of synthesis of this hormone tends to decrease in people over the age of 75 years, being much lower when compared to people aged 20 to 30 years (REITER and ROBINSON, 1996).

RESULTS AND DISCUSSIONS

Characterization: Fibromyalgia is a syndrome characterized by chronic widespread pain. It was first described more than 100 years ago, when the American College of Rheumatology published official diagnostic guidelines in 1990. However, the first treatment guidelines were published 15 years later by the American Pain Society. Since then, many controversies have surrounded both the diagnosis and treatment of fibromyalgia syndrome. Although the condition imposes a considerable impact on the patient, no medical specialty has yet been claimed for this disease. These patients are most frequently assisted by rheumatologists (DYMON, 2015). It is a common cause of musculoskeletal pain; it is defined as a disease that mainly affects the muscles. Fibromyalgia syndrome affects about 2% to 4% of the adult population in accidental countries, and women are 5 to 9 times more affected than men. The predominant age of onset of symptoms ranges from 20 to 50 years. As for children, there are citations of cases with 2 years of age and also in individuals over fifty years of age (CLAUW, 2015). In 1990, the American College of Rheumatology made a standardization for diagnostic studies of patients with this disease. Diagnostic criteria include the presence of generalized pain (defined as pain on the right and left side of the body, both above and below the waist for at least three months (CLAUW, 2015). Fibromyalgia is also known as JoninaDognini Syndrome, a syndrome characterized by diffuse muscle pain, fatigue, sleep disorders, paraesthesias, subjective edema, cognitive disorders and pain at specific points under pressure (points on the body with increased sensitivity or tender-points) (WILLIAMS; CLAUW, 2009). The causes of fibromyalgia are still unknown, but there are some factors that are often associated with this syndrome. Among these factors,

genetic predisposition and stress can be considered. Fibromyalgia is very recurrent in people of the same family, which may be an indicator that there are some mutations capable of causing the syndrome. It is a complex and very common disease. It mainly affects women. It is characterized by pain in different parts of the body. Research has focused on the study of genes associated with the function of the autonomic nervous system, in particular, variations in the gene that gives rise to the enzyme responsible for deactivating adrenaline, catechol-O-methyltransferase (WOOF, 2011).

Function of Melatonin: As for the function of melatonin, it is considered one of the most versatile and potent substances in the body, presenting multiple functions. It is produced in the pineal gland exclusively during the night. The essential functional characteristic of this system is that it is strictly controlled by the circadian timing system. The production of melatonin is directly linked to the presence of light. When light falls on the retina, the optic nerve and other neuronal connections take this information to the pineal gland, inhibiting the production of melatonin. The highest production of melatonin occurs at night between 2 and 3 am, at a normal pace of life, and this increased production leads to sleep. Thus, melatonin has an action in inducing sleep, in addition to being a potent antioxidant and immune system booster (REITER and ROBINSON, 1996). In the treatment of sleep disorders, melatonin has its established use in medical clinics, as an antioxidant (protecting DNA from attack by free radicals), anti-amyloidogenic, neurotrophic and neuroplastic, being used as an auxiliary treatment in neurological and degenerative diseases (HOHL; MANCINI; HALPERN, 2016). It can also be mentioned, stimulation of an aged immune system, cardiovascular protection, stabilization of the body's biological rhythms, restoration of the night cycle of rest and recovery, stimulation of growth hormone and reduction of symptoms of depression. Thus, melatonin or its analogs have been used in the treatment of certain types of migraine, in depressive disorders, anesthesia, as an adjunct in antitumor and / or antimetastatic treatment, as a powerful limiting agent for post-ischemic injuries (associated with hypothermia in the case of perinatal hypoxia and ischemia, in premature bronchopulmonary dysplasia, stroke), in metabolic diseases, polycystic ovary syndrome, etc. (HOHL *et al*., 2016).

There is solid experimental evidence showing that melatonin acts by regulating each step of the energy balance: food intake, the flow of energy to and from stocks, and energy expenditure. It is a hormone that, mainly by central action, regulates food intake by reducing it, albeit slightly; regulates the production and secretion of insulin, glucagon and cortisol, thus organizing the flow of energy reserves to and from stocks; and, more importantly, it increases energy expenditure, increasing the mass and activity of brown adipose tissue and increasing the browning of white adipose tissue. It can, therefore, be seen as yet another antiobesogenic hormonal factor (HOHL *et al*., 2016). More recently, melatonin has been recognized as a potent endogenous antioxidant (TAN *et al*., 2003). Studies have shown that this hormone effectively protects macromolecules, tissues, organs and organisms against oxidative damage, acting at different levels, including the attenuation of free radicals (HARDELAND, 2005). These effects are due both to the direct interaction of the melatonin molecule with reactive oxygen and nitrogen species, as well as by increasing the expression of antioxidant enzymes such as glutathione oxidase and peroxidase, and also by decreasing the expression of prooxidative enzymes with synthases and lipoxygenase (HARDELAND, 2005; HARDELAND *et al*., 2006). This hormone does not act only through interaction with specific receptors. Its primary action is to act as a potent reducer of the number of hydroxyl radicals, considered the most powerful toxic reactive species of oxygen, being configured as a more potent anti-free radical agent than glutathione and mannitol. In view of its presence in the nucleus, this indicates its protective role of DNA. An important aspect to be mentioned is the role of melatonin in neuroprotection, antioxidant actions are observed at different levels, including attenuation of the formation of radicals by anti-excitatory and anti-inflammatory effects. This is not restricted to cleaning, although melatonin interacts effectively with various species of reactive oxygen and nitrogen, as well as with organic radicals, but includes the positive regulation of antioxidant enzymes (by glutathione oxidase, glutathione reductase, - glutamylcysteine synthase, glucose -6-phosphate dehydrogenase, sometimes Cu, Zn and superoxide Mn-superoxide and catalase) and infra-regulation of pro-oxidant enzymes (NO synthases, lipoxygenases) (HARDELAND, 2005; HARDELAND *et al*., 2006).

To use melatonin as a sleep-inducing agent, one must initially observe the conditions of the individual (temperature, drowsiness, among others) and the environment (lights on, posture during sleep, among others) at the time of administration, as influence its effectiveness, regardless of dose. Melatonin can be used to induce sleepiness during the day in healthy people, including through intranasal administration (VOLLRATH *et al*., 1981). This can happen due to the increase in melatonin levels, which is related to increased drowsiness and decreased body temperature, which provides sleep. It is believed that the reduction in body temperature probably occurs through its action of melatonin in its receptors in peripheral blood vessels, resulting in vasodilation, inducing sleep in the individual (VAN SOMEREN, 2000). According to Dollins (1994), the administration of 2 mg of melatonin at 17:00 hours without any control of the ambient light or the patient's posture causes drowsiness only after about 3 to 4 weeks, while small doses (0, 1 to 10 mg) administered to subjects in decubitus and in low light induce sleep quickly. According to Arendt and Skene (2005), the soporific effect of melatonin seems to be more evident when its endogenous circulating level is minimal (during the day) and its administration in the morning delays the onset of nocturnal drowsiness by delaying the circadian rhythm (phase delay) (SOUZA NETO and CASTRO, 2008).

Melatonin Receptors: As for melatonin receptors, three types of membrane receptors are mentioned. The first one is known as a high affinity receptor, Mt1 also called (MTNR1A or Mel1A) and MT2 (MTNR1B or Mel 1B), these belong to the superfamily of receptors linked to protein G. According to Hohl, Mancini and Halpern (2016), the receptors bind to the Gi or Go proteins and can promote a reduction in the production of cAMP (VIDOR, 2010). As for MT1, it is observed that this receptor has an affinity for Gq or G11 proteins, activating phospholipase C, increasing the production of diacylglycerol and lP3, and may, consequently, increase the intracellular concentration of calcium and PKC activity. The mechanisms mobilized by Gi, when activating the MT2 receptor, can also result in a reduction in cGMP (VIDOR, 2010). These high affinity receptors are distributed throughout the organism from the central nervous system, where it is present in many

structures, to the periphery of the organism, being found in many organs and tissues. Regarding the third type of membrane receptor for melatonin, MT3 is mentioned, which is present in all mammals. It is a receptor whose molecular structure is very similar to an enzyme, quinone reductase, and whose actions are not completely understood (HOHL *et al*. 2016).

Chronic Pain: Chronic pain is a debilitating disease of a multifactorial nature with disastrous consequences, affecting the physical, psychological and behavioral aspects (VIDOR, 2010). Among these, chronic musculoskeletal pain causes enormous suffering and people affected have reduced quality of life and functional capacity for activities of daily living, in addition to having a higher incidence of depressive symptoms and anxiety and negative thoughts about life (VIDOR, 2013). The disease affects 30% of the world population. Statistics from the World Health Organization-WHO show that 75 to 80% of affected people seek the health system for pain and that 20 40% of adults suffer from some type of chronic pain, causing absences, contributing to absenteeism and consequently reducing productive capacity in the world of work. It is likely that an excess of adrenaline plays a major role in the development of fibromyalgia. However, it is necessary to emphasize that genetic alterations are only a predisposing factor, a fertile ground on which, with favorable (or unfavorable) conditions, it is possible to develop fibromyalgia. In no way is genetic alteration the cause of the disease (MARTINEZ-LAVIN, 2014).

Definition of Fibromyalgia: The development of fibromyalgia is associated with stressors, which can be physical, infectious or emotional. Therefore, it is important to understand several concepts associated with stress. The term stress is ambiguous. If used to designate the cause of a phenomenon, then we speak of a stressor, but it also refers to the effect of a phenomenon. In that case, we say that a person is stressed. The most accepted definition of stress consists of any stimulus, whether physical or emotional, that attacks the balanced and harmonic function of our body. Seyle (1946) conceptualized stress as "the body's non-specific response to any demand, whether caused by, or resulting in, favorable or unfavorable conditions". To these reactions Selye called General Adaptation Syndrome, with three distinct phases and currently identified as: (1) Alarm or alert, where there is a rupture of the organism's internal balance and the mobilization of it to face the stressor. This rapid response is mediated mainly by the activation of the sympathetic autonomic nervous system, which promotes the release of neurotransmitters in several target organs and also stimulates the medulla of the 23 adrenal glands to release the catecholaminergic hormones, adrenaline and norepinephrine, further reinforcing neural activation (DOLAN, 2006). The term distress was coined by Seyle (1946) as the non-adapted response to the stress that produces physical or emotional damage. Negative stress or distress is excessive stress, which occurs when a person exceeds his limits and exhausts his ability to adapt. Dolan (2006) defines distress as dangerous stress, being the chronic activation of the organism to try to adapt to a situation interpreted as a threat and which does not follow deactivation or the perception of accomplishment. The impact on quality of life is strongly correlated with the intensity of pain, fatigue and decreased functional capacity (MARTINEZ *et al*., 1995). Fibromyalgia must be recognized as a complex and heterogeneous state of health in which there is a disturbance in pain processing associated with other secondary characteristics (CARVILLE, 2008). The diagnosis of fibromyalgia is exclusively clinical and eventual subsidiary exams can be requested only for differential diagnosis. The diagnosis must be confirmed at the beginning of the treatment, so that it is possible to clarify to the patient what is true and what is false.

Patient orientation is a critical factor for optimal fibromyalgia control. As an initial part of the treatment, the patient should be provided with basic information about fibromyalgia and its treatment options, guiding them on pain control and self-control programs (BUCKHARDT *et al*., 2005). The American College of Rheumatology, in 1990, published classification criteria for fibromyalgia. These criteria were also validated for the Brazilian population. Among the criteria, there is a painful sensitivity in pre-established anatomical sites, called tender points, which will be presented below, in the description of the clinical picture (ATALLAH-HAUN *et al*., 1999). The proportion of women to men is approximately 6 to 10: 1. The highest prevalence is between 30-50 years old, which can also occur in childhood and old age. It can be associated with 25% of rheumatoid arthritis, 30% of systemic lupus erythematosus and 50% of Sjogren's syndromes. The recognition of this concomitance is extremely useful, as it will allow a more adequate therapeutic orientation (PROVENZA *et al*., 2004).

A complete understanding of fibromyalgia requires a comprehensive assessment of pain, function and the psychosocial context (CARVILLE, 2008). In addition to pain, it is important to assess the severity of other symptoms such as fatigue, sleep disorders, mood, cognition and their impact on the patient's quality of life (BUCKHARDT *et al*., 2005).

Diagnosis and Treatment: The strategy for the ideal treatment of fibromyalgia requires a multidisciplinary approach with the combination of non-pharmacological and pharmacological treatment modalities. The treatment must be elaborated, in discussion with the patient, according to the intensity of his pain, functionality and characteristics (CARVILLE, 2008), it is also important to take into account his biopsychosocial and cultural issues. In general, the diagnosis of fibromyalgia can be made by verifying the number of specific pain points. If in eighteen pain points, if there is severe pain in at least eleven or more, the diagnosis is confirmed (PETZKE *et al*., 2003 a; PETZKE *et al*., 2003b). Treatment consists of physical therapy, exercise, massage, cognitive behavioral therapy, as well as analgesic, antidepressant, antiepileptic, and relaxing and sleep-inducing drugs. Among the latter, melatonin, which is a hormone produced by the Pineal gland, has been used with remarkable improvement in symptoms, according to the researchers' report (CLAUW, 2015). Central symptoms that accompany the painful condition are non-restorative sleep and fatigue, present in the vast majority of patients.

Conclusion

It can be seen in this literature review, that melatonin has demonstrated an effect in reducing or inhibiting pain in fibromyalgia, both administered alone and associated with other drugs. It can be seen, through a thorough review, that melatonin acts strongly as an antinociceptive agent. The verification of the diagnoses for fibromyalgia revealed that, with the knowledge currently available, such diagnoses cannot be made directly, but to the exclusion of other diseases. This highlights the need for further research to find a more direct diagnosis. Several types of sleep disorders have been reported,

resulting in an absence of energy restoration and consequent tiredness, which appears early in the morning (PROVENZA *et al*., 2014). Fatigue can be quite significant, with a feeling of easy exhaustion and difficulty in performing work or household tasks. Paresthetic feelings are usually present. It is important to highlight that the paresthesias in these patients do not respect a dermatological distribution (LESSARD and RUSSELL, 1992). In the treatment of Fibromyalgia, amitriptyline is recommended among the tricyclic compounds, and among muscle relaxants, cyclobenzaprine which reduces pain and often improves the ability to function. The use of aminotriptyline is widely used, in addition to duloxetine, fluoxetine, milcacipran and other medications such as cyclobenzapine, gabapentin, pregabalin and tramadol. The use of serotonin reuptake inhibitors, such as fluoxetine, in combination with tricyclics is also recommended in the treatment of fibromyalgia (BUCKHARDT *et al*., 2005). The isolated use of other serotonin reuptake inhibitors, such as sertraline, paroxetine, citalopram and escitalopram, were not recommended by the Society of Rheumatology. The most recommended treatments with melatonin are based on the use of this substance alone or in combination with other compounds. However, other dosages and association with other drugs should be tested, aiming at better efficacy in the treatment of patients with fibromyalgia. Although several studies have been developed showing the effectiveness of this hormone in the treatment of fibromyalgia, in delaying aging and in the regulation of sleep, research still needs to be developed in order to reveal aspects not yet known of the melatonin - pain interaction, such as variations in its administration to the patient, including dosage, age and other aspects. Therefore, it is necessary that more studies are developed trying to evaluate the antinociceptive action of melatonin, especially in fibromyalgia, in addition to other uses for this hormone.

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