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The Physiological and Pharmacological Roles of Melatonin and Pregabalin

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Melatonin and pregabalin are two important compounds that are broadly used in the fields of physiological and medicinal sciences. Melatonin is a primary hormone mainly secreted by the pineal gland and plays an important role in regulating circadian rhythms, sleep-wake cycles, and neuroimmune processes. Its strong antioxidant anti-inflammatory and anti-apoptotic properties have protected it against a wide range of diseases, from cancer to neurological disorders. In this study, the synthesis of melatonin will be widely studied, mainly regarding its role in regulating circadian rhythms and sleep, and its possible therapeutic use in treating neurological diseases and inflammation-related disorders.

Pregabalin is an analog of the neurotransmitter gamma-aminobutyric acid (GABA), with anticonvulsant, analgesic, and anxiolytic actions. Clinical practice has widely utilized it because studies indicate that it is useful in treating a variety of conditions: fibromyalgia, epilepsy, neuropathic pain, and generalized anxiety disorder. This article reviews aspects of the pharmacokinetics of pregabalin, its useful functions in pain treatment, and its impact on calcium channel regulation. The review also discusses indications of pregabalin in therapy, along with its possible side effects. This review article aims to consider the molecular processes underlying the activities of melatonin and pregabalin and their therapeutic potential for the management of sleep disorders, inflammation, and neurological diseases to future use of these compounds clinically.

Keywords: Melatonin; pregabalin; therapeutic; inflammatory; Circadian rhythm.

1. INTRODUCTION

Melatonin, also known as N-acetyl-5-methoxytryptamine, is a hormone primarily released by the pineal gland of animals that has a role in the control of circadian rhythm, sleep, and neuroimmune modulation (Xie et al., 2020). Many mammalian tissues and organs, including the skin, gastrointestinal, immunological, and genitourinary systems, also generate melatonin (Calvo and Maldonado, 2016). Melatonin regulates pubertal development, the sleep-wake cycle, and seasonal adaptability (Pandi-Perumal et al., 2018). Melatonin directly affects hippocampal neurons, which regulate memory formation (Comai and Gobbi, 2014). Melatonin has antinociceptive, antidepressant, anxiolytic, and antixenophobic effects (fear of new things) (Uz et al., 2015). Melatonin has antioxidant, anti-tumor, anti-inflammatory, pain-modulating, blood pressure-lowering, retinal, vascular, seasonal reproductive, and osteoblast differentiation properties (Li et al., 2013; Comai and Gobbi, 2014). Melatonin and its metabolites have a high potential to bind free oxygen radicals, preventing inflammation and apoptosis (Reiter et al., 2018).

Apoptosis, which translates from Greek as "falling off or dropping off," is a crucial process for the growth of healthy organs. Apoptosis is defined morphologically by nuclear shrinkage, chromatin condensation, and DNA fragmentation into oligonucleosome-sized fragments, whereas the plasma membrane and intracellular organelles are unaffected (Saraste and Pulkki, 2020). Recent research suggests that mechanisms involved in pulmonary diseases such as lung cancer, interstitial pulmonary fibrosis, and adult respiratory distress syndrome (ARDS) may also be significantly influenced by apoptosis (Martin et al., 2013; Fine et al., 2020). The normal and aberrant control of cell death resulting to apoptosis in pulmonary epithelial cells is governed by various factors, each likely to differ in a given context (Adams, 2013).

Pregabalin is a structural counterpart of the naturally occurring transmitter GABA. It is currently being researched for the treatment of generalized anxiety disorder, neuropathic pain, and epilepsy (Ben-Menachem and Kugler, 2020). According to recent research, pregabalin has a strong anticonvulsant effect and a good pharmacokinetic profile. Pregabalin has been demonstrated to be a highly successful and well-tolerated supplementary medication in treating patients with partial seizures, whether or not they

have subsequent generalization, in clinical trials (Ben-Menachem and Kugler, 2020). Pregabalin is a substrate of the system L transporter, which carries large amino acids between the gut and brain. In line with this, preclinical research using mice, rats, and monkeys has demonstrated that pregabalin rapidly crosses the blood-brain barrier. This is significant for a substance that affects central nervous system (CNS) activity (Kugler, 2020).

Note: Melatonin and pregabalin have a meaning in both physiological and pharmacological sciences because of their therapeutic benefits in different pathological states, especially for neurological health. Both compounds have neuroprotective properties; melatonin maintains circadian rhythms and immune functions, while pregabalin acts directly on neurotransmitter pathways to alleviate symptoms of various neurological disorders. Their combined therapeutic roles, therefore, point toward possible synergy in sleep disturbances, inflammation, and neurological conditions. Thorough studies are warranted to elucidate long-term effects and its clinical use.

2. MELATONIN

Melatonin which is otherwise referred to as N-acetyl-5-methoxytryptamine, is a chemical generated from tryptophan that is found in large quantities in both plant and animal sources, including human milk, bananas, beets, cucumbers, and tomatoes. Melatonin is predominantly generated by the pineal gland in humans, although it is also produced by the retina and the gastrointestinal tract (Hirsch-Rodriguez et al., 2017). Melatonin, in addition to being produced by the pineal gland, is also produced by the brain, liver, kidney, adrenal gland, heart, thymus, genital glands, placenta, and uterine (Acuna-Castroviejo et al., 2014; Cipolla-Neto and Amaral, 2018). The enzymes N-acetyltransferase (NAT) and hydroxyindole O-methyltransferase (HIOMT) produce serotonin from the amino acid tryptophan by hydroxylation and decarboxylation. Serotonin is then transformed into melatonin.

2.1 Synthesis of Melatonin

Amino acid L-tryptophan is taken up by the gland as the first step in the production of melatonin. L-tryptophan, tetrahydropteridine: oxygen oxidoreductase, catalyzes the conversion of L-tryptophan to 5-hydroxytryptophan, which is then decarboxylated by L-aromatic amino acid decarboxylase (aromatic L-acid carboxylase) to serotonin. The crucial enzyme in the synthesis of melatonin, arylalkulamine N-acetyltransferase (acetyl CoA:aryl-amine N-acetyltransferase) [16], completes the subsequent step, which is the N-acetylation of serotonin to N-acetylserotonin. The route is completed by the enzyme hydroxyindole-O-methyltransferase (S-adenosyl-L-methionine: N-acetylserotonin-O-methyltransferase) which O-methylates N-acetylserotonin to melatonin (Li et al., 2013).

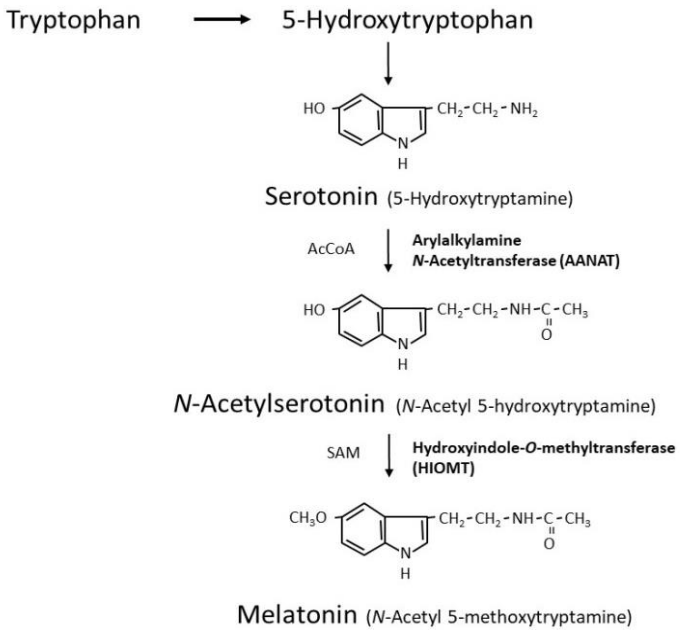

Fig. 1. Synthesis of Melatonin (Li et al., 2013)

Melatonin is not kept in pineal cells after it is produced; instead, it is swiftly discharged into the bloodstream (Reiter et al., 2018). In addition to the blood, melatonin can also be found in saliva, cerebrospinal fluid, bile, semen, and amniotic fluid. The average daily production rates of endogenous melatonin have been estimated to be around 30 g (Cipolla-Neto and Amaral, 2018; Hardeland, 2018). Numerous studies have estimated that the half-life of melatonin in serum is between 30 minutes and one hour or less (Li et al., 2013; Acuna-Castroviejo et al., 2014).

The liver and kidneys are where melatonin is processed predominantly and secondly, respectively. It undergoes 6-hydroxylation to 6-hydroxy melatonin, which is then conjugated to produce 6-hydroxy melatonin sulfate (90%) or 6-hydroxy melatonin glucuronide (1%). The amount of unmetabolized melatonin discharged in urine is around 5% of serum melatonin level. Smaller metabolites such as cyclic 2-hydroxy melatonin, N-gamma-acetyl-N-2-formyl-5-methoxykynurenamine, and N-gamma-acetyl-5-methoxykynurenamine are also produced by melatonin (Li et al., 2013; Acuna-Castroviejo et al., 2014; Cipolla-Neto and Amaral, 2018].

2.2 Melatonin Receptors

Melatonin receptors are located in the following parts of the body: the brain, retina, cardiovascular system, cardiac ventricular wall, aorta, coronary and cerebral arteries, liver and gallbladder, duodenal enterocytes, colon, cecum, appendix vermiform is, skin, parotid gland, exocrine pancreas, kidney, cells of the immune system, platelets, brown and white adipocytes, epithelial (Hardeland, 2021). Melatonin receptors are most frequently located in the jejunal and colonic mucosa of the gastrointestinal tract (Pandi-Perumal et al., 2018).

There are different membrane receptors and nuclear receptor:

Melatonin receptor type 1a: Mel 1a, ML1a, ML1, MT1, MTNR1A It is encoded in human chromosome 4 and consists of 351 amino acids (Li et al., 2013). MT1 receptor constitutes adenylate cyclase inhibition by binding to various G-proteins (Uz et al., 2015). Human skin frequently contains MT1 receptors (Pandi-Perumal et al., 2018). In the brain and suprachiasmatic nucleus (SCN), MT1 receptor expression declines with aging and Alzheimer's disease (Pandi-Perumal et al., 2018). Mel 1a, ML1a, MTNR1A, and ML1a neuronal levels are decreased by MT1 receptors. On human chromosome 4, it is encoded as a 351 amino acid protein (Li et al., 2013). The MT1 receptor inhibits adenylate cyclase by interacting with several G-proteins. SCN discharge rate and prolactin secretion inhibition (Dubocovich et al., 2013).

Melatonin receptor type 1b: MT2, ML1b, Mel 1b, and MTNR1B It is 363 amino acids long and encoded on human chromosome 11 (Li et al., 2013). The MT2 receptor binds to numerous G-proteins to produce adenylate cyclase inhibition. It also blocks the soluble guanylyl cyclase pathway (Li et al., 2013). The generation of cyclic AMP (cAMP) is decreased as a result of adenylate cyclase inhibition brought on by melatonin receptor activation (Levoye et al., 2016; Chaste et al., 2021).

MT2 receptors are found in both healthy and abnormal melanocytes as well as eccrine sweat glands in the skin (Pandi-Perumal et al., 2018). In the hippocampus of rats, MT2 receptors prevent GABA-A receptor-related activities (Dubocovich et al., 2013). The expression of the MT2 receptor is decreased in Alzheimer's disease. Involvement of MT2 receptors in antidepressant action (Hardeland, 2021).

The pathophysiology and pharmacology of sleep problems, anxiety, depression, Alzheimer's disease, and pain are all influenced by MT2 receptors (Comai and Gobbi, 2014). Potential novel targets for the creation of hypnotic drugs include MT2 receptors (Comai and Gobbi, 2014). The effects of melatonin that reduce anxiety are caused by MT2 receptors. Pharmacological investigations have shown that MT2 receptors, in particular NREMS, control sleep (Comai and Gobbi, 2014). Comparing MT2 receptor ligands to non-selective MT1/MT2 ligands, MT2 receptor ligands exhibit stronger hypnotic effects (Comai and Gobbi, 2014).

Mel1c, MTNR1C: Humans do not possess it. Fish, amphibians, and birds all contain it (Li et al., 2013). In contrast to MT1 and MT2, the MTNR1C receptor in chicken has a different rhythm. Its intensity is greatest during the day and is at its lowest at night (Li et al., 2013; Rada and Wiechmann).

MT3, ML2= NQO2= Quinone reductase 2 enzyme= QR: This enzyme is a member of the reductase group, which works to prevent

oxidative stress by preventing quinones' electron transfer reactions (Pandi-Perumal et al., 2018). This enzyme, also known as the MT3 receptor, is found in the tissue of the liver, kidney, heart, lung, gut, muscle, and brown fat. It is an enzyme for detoxification (Ekmekcioglu, 2016). Its involvement in managing intraocular pressure is supported by evidence (Ekmekcioglu, 2016).

RZR/RORα: Melatonin binds to the transcription factors in the nucleus that are members of the retinoic acid receptor super-family through the retinoid-related Orphan Nuclear Hormone Receptor. For retinoic acid receptor super-family variations, the following are described; ROR (retinoic acid receptor-related Orphan receptor; human gene ID: 6095) includes ROR isoforms a (aka ROR1), b (aka ROR2), and d (also known as RZR), as well as ROR (aka RZR; human gene ID: 6096), the gene's product (Pandi-Perumal et al., 2018).

GPR50: H9, ML1X: Orphan receptor associated with melatonin. The term "X linked Orphan G-protein coupled" (It binds to G-protein and is an X-linked inherited receptor. It is an orthologue of the non-mammalian living organism MEL1c [24]. Its gene has 618 amino acids and is found on the X chromosome (Xq28) (Li et al., 2013). All mammalians, including humans, have it. It lacks the properties necessary to bind to melatonin (Ekmekcioglu, 2016). However, it is effective in binding of melatonin to MT1 (Hirsch-Rodriguez et al., 2017). GPR50 is not present in birds and fish (Li et al., 2013). It is located in the brain and periphery. Its natural ligand has not been defined yet. It was reported that a deletion mutant in GPR50 might have been associated with bipolar disorder and major depression (Thomson et al., 2015). GPR50 has no affinity to melatonin; however, when it dimerizes with MT1, it inhibits the melatonin signal (Levoye et al., 2016; Chaste et al., 2021). GPR50 has other functions apart from melatonin (Li et al., 2013). GPR50 interacts with neurite outgrow inhibitor (NOGO-A) (Grunewald et al., 2019) and TIP60 (glucocorticoid receptor signal coactivator and histone acetyltransferase) (Li et al., 2013; Reiter et al., 2018).

After MT1 and MT2 receptors adhere to the cell surface, they create their effects through G-protein. Activation of MT1 receptor leads to inhibition of cAMP formation which was stimulated by forskolin, together with inhibition of Protein kinase A (PKA) (Ekmekcioglu, 2016). Similarly, activation of MT2 receptor leads to inhibition of cAMP formation, which was stimulated by forskolin (Ekmekcioglu, 2016). Additionally, it inhibits formation of cGMP (Ekmekcioglu, 2016). While membrane receptors are basically located in the central nervous system, RZR/RORα is located at both periphery and the brain (Carlberg, 2020). Membrane receptors and their specific agonists are associated with circadian rhythm, whereas RZR/RORα seems to be responsible for immunomodulation at the periphery, cellular growth and differentiation of bone (Carlberg, 2020). Activation of Protein kinase C-α is a critical step in the formation of melatonin effect (Pandi-Perumal et al., 2018). Development of pharmacological agents, which are effective on MT receptors, may be associated with antihypertensive, anti-cancer or immunostimulant effects or they may facilitate falling asleep (Ekmekcioglu, 2016). In addition to its anti-inflammatory effect, its immunostimulant effect is an undesired situation in autoimmune disorders and melatonergic drugs may be contraindicated in such patients (Hardeland, 2021). For example, melatonin aggravates the symptoms of rheumatoid arthritis by stimulating proinflammatory cytokines (Forrest et al., 2017).

2.3 The Role of Melatonin

An essential physiological sleep regulator in nocturnal species, such as humans, is melatonin. In most cases, endogenous melatonin production in humans begins two hours following the sudden nighttime increase in sleep inclination (Zisapel, 2017); The duration of nocturnal melatonin also informs the brain and other organs, including the suprachiasmatic nucleus (SCN), about the length of the night. In both normal and blind patients, the circadian melatonin rhythm is tightly correlated with the sleep rhythm (Zisapel, 2017).

When melatonin is administered throughout the day (when it is not naturally present), it makes people feel tired and sleepy (Gorfine et al., 2016). It's important to note that melatonin is not sedative: in nocturnally active animals, melatonin is associated with wakefulness rather than periods of sleep, and in humans, its sleep-promoting effects start to become noticeable about two hours after consumption, mimicking the physiological process at night (Zisapel, 2017). When intrinsic melatonin levels sufficiently rise, the outcome of extrinsic melatonin are less obvious and is best exhibited when intrinsic melatonin levels are low (for example, during the

day or in people who manufacture insufficient quantities of melatonin) (Tordjman et al., 2013).

Additionally, melatonin promotes weariness and changes in precuneus activation that resemble sleep via acting on default mode network (DMN) areas in the brain (Gorfine et al., 2016; Gorfien and Zisapel, 2019). When not doing a task-dependent task, the default mode network (DMN) is a network of brain areas that is active during rest (Raichle et al., 2021). It is involved in sensitive awareness and daydreaming and is made up of the medial prefrontal cortex, posterior cingulate cortex, precuneus, inferior parietal lobe, lateral temporal cortex, and hippocampal formation (Spreng et al., 2020). The precuneus is implicated in many complex processes within this network, including recall and memory, information integration (gestalt) related to perception of the environment, cue reactivity, mental imagery techniques, retrieval of episodic memories, and affective reactions to pain (Cavanna and Trimble, 2016). Connectivity within the DMN declines during SWS and while sleeping (Horovitz et al., 2019).

When healthy young people are administered melatonin in the afternoon, activation in the precuneus, which is situated at the rostro-medial region of the occipital cortex, is reduced. These results align with estimates of subjective weariness (Gorfine et al., 2016). Exogenous melatonin injection at night has no additional discernible effects since the activity of this brain region is diminished concurrently with the endogenous rise of melatonin (Arbon et al., 2015). The homeostatic sleep pressure marker SWS, which is not increased by melatonin (Zisapel, 2017), suggests that the circadian component of sleep regulation is primarily responsible for melatonin's ability to promote sleep.

The homeostatic sleep pressure marker slow-wave sleep (SWS), which is not increased by melatonin (Zisapel, 2017; Arbon et al., 2015), suggests that the circadian component of sleep regulation is primarily responsible for melatonin's ability to promote sleep.

2.4 Melatonin and Circadian Rhythm

Understanding the normal physiology of sleep is imperative to understanding dysfunctional sleep and circadian rhythms. Humans need and benefit from sleep, which is a physiological process governed by circadian rhythms. These daily biological cycles known as circadian rhythms regulate a huge number of physiological activities (Circadian Rhythms, 2020).

The entraining of "endogenous oscillators," which are made up of neuronal, hormonal, and genetic components, has been shown to have a significant impact on circadian rhythms under both natural and artificial light (Redlin, 2021).

The circadian system contains both central and peripheral oscillators, each of which has a distinct function. The suprachiasmatic nucleus (SCN), a paired nucleus in the hypothalamus of humans and other mammals that receives input from certain retinal neurons, is the main central oscillator (Carlson, 2020). The SCN rhythm is used to operate peripheral oscillators. The 20,000 neurons that make up the SCN's rhythm are controlled by the cyclical expression of clock genes (Reiter et al., 2018). Clock genes produce clock proteins, transcriptional regulators "whose levels oscillate or cycle in a predictable manner" (Reiter et al., 2018).

The process begins when the pineal gland, an effector of various physiological processes, receives stimulation from the SCN via a neurological channel. Through descending hypothalamic projections, the SCN signals the medial forebrain bundle to start this route. The superior cervical ganglia are then reached by the medial forebrain bundle through the spinal cord. The pineal gland is then sympathetically innervated by the superior cervical ganglia [38]. Intrinsically photosensitive retinal ganglion cells (ipRGCs), a particular type of retinal cell, detect light and transmit information about light intensity and wavelength to the SCN via the Retin hypothalamic tract. This pathway enables the pineal gland, which regulates melatonin metabolism, to receive light signals (Fig. 2).

Light strikes the retina, which results in a neuronal signaling cascade from the retina to the Retin hypothalamic tract (RHT) to the suprachiasmatic nucleus (SCN) to the paraventricular nucleus (PVN) to the brainstem to the spinal cord (levels T1-T3) to the superior cervical ganglion (SCG) to the pineal gland.

It is well known that melatonin aids in inducing sleep. Because of this, low or absent melatonin levels should keep people alert. Melatonin's ability to circulate in the circulation is already known to be suppressed by exposure to light, particularly high-wavelength light (Redlin, 2021). The inhibition of melatonin-synthesizing enzymes

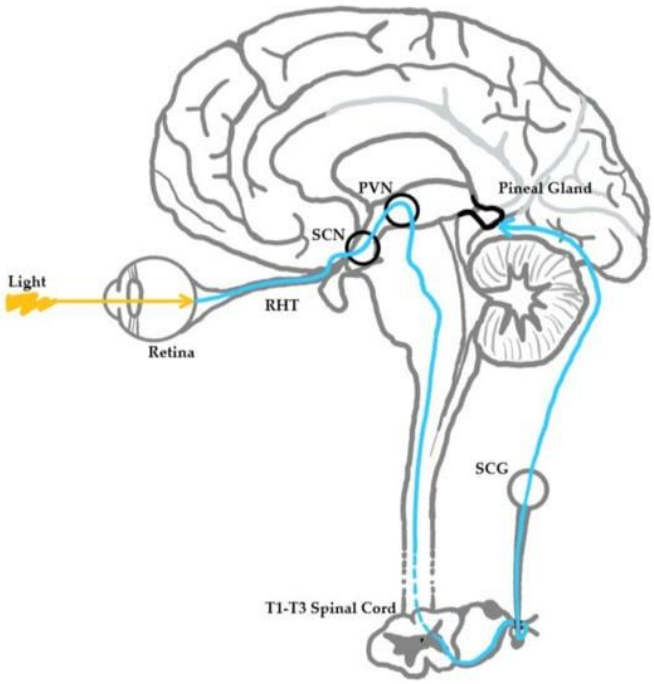

Fig. 2. Neuroanatomical pathway of light stimulus to the pineal gland

like N-acetyltransferase in the pineal gland that are influenced by ambient light is assumed to be the cause of the suppression of plasma melatonin (Redlin, 2021).

Typically, this procedure prevents drowsiness throughout the day, when persons who live a diurnal lifestyle must be active. But exposure to high-energy light at odd hours throws off circadian cycles and unnecessarily reduces melatonin production and secretion in the pineal gland (Paul et al., 2015; Reiter et al., 2016). There are numerous instances of aberrant light exposures that people encounter regularly. Living close to the poles of the planet, where light or darkness might endure for weeks at a time, is one of them. The people who live closest to the poles endure weeks at a time of complete darkness or nonstop sunlight. There are 110 consecutive days of darkness in the winter and 110 consecutive days of light in the summer at Halley, Antarctica (Pattyn et al., 2017). People have been shown to have decreased slow-wave sleep (SWS), increased stage R sleep, and fragmented sleep as a result of these light circumstances (Resuehr et al., 2019).

There, researchers complain of having trouble sleeping, but a group discovered that phototherapy, which involves exposure to standard white and blue-enriched light throughout the day, can correct sleep timing delay (Pattyn et al., 2017). Exogenous melatonin administration at the right periods has also been found to be useful in enhancing subjective sleep measures, but not objective sleep parameters (Arendt and Middleton, 2018). The abnormal melatonin rhythm in these people was repaired by appropriate light exposure during the prolonged period of low light.

A subset of contemporary nighttime artificial light, rotating or night shift work exposes workers to light at unsuitable periods. Night shift nurses' cortisol, body temperature, and melatonin cycles are out of sync with studies on nocturnal light (Razavi et al., 2019) and produce less melatonin (Zhang and Papantoniou, 2019).

Another frequent occurrence of inappropriate light exposure is the usage of light-emitting technologies and increased global ambient light. Mobile devices such as cell phones, tablets, computers, and televisions all emit light. Increasing ambient light and light-emitting technology use exposes humans to light at inappropriate times. Since the introduction of the first electrical lighting system in New York in 1882, the amount of light in the environment has significantly increased, to the point where humans no longer follow the cycles of natural light and dark (Tähkämö et al., 2019). This luminous infiltration has also been referred to as light pollution and light poisoning. LAN from

artificial sources was recognized as an environmental pollutant as early as 1980 (Tähkämö et al., 2019).

Numerous investigations have demonstrated that a key element in the suppression of melatonin is the light's wavelength. In particular, because the short wavelength has been demonstrated to decrease melatonin (Lockley et al., 2013; Green et al., 2017), the human circadian pacemaker in the SCN is more sensitive to short or blue wavelength light (460 nm) than long or red wavelength light (555 nm). Although less so than light wavelength, light intensity has a detrimental impact on sleep (Knufinke et al., 2019). As an alternative, restricting exposure to short-wavelength light has been demonstrated to improve sleep quality, reduce sleep onset latency by 7 minutes, and improve alertness the next morning (Lewis et al., 2018).

2.5 Effects of Melatonin

2.5.1 Anti-inflammatory effect of melatonin

When an injection causes bodily harm or when the body is stimulated chemically or physically, the body naturally responds by inducing inflammation. Inflammatory tissue repair is facilitated by inflammatory cells that emit TNF-, IL-1, and IL-6, including leukocytes, macrophages, mast cells, and endothelial cells (Puig et al., 2016). One of the key tactics in combating chronic or acute inflammatory disorders, such as pneumonia, asthma, and COPD, is the inhibition of the inflammatory process (Puig et al., 2016; Peng et al., 2018).

Furthermore, MT treatment inhibits inflammatory processes such as nitric oxide (NO) release, cyclooxygenase-2 activation, the NLRP3 inflammasome, toll-like receptor 4 (TLR-4) and mTOR signaling, and amyloid-toxicity (Wang et al., 2018; Aguilar et al., 2019). Furthermore, earlier research demonstrated that exogenous MT reduced the inflammatory response by upregulating the expression of Silent Information Regulator 1 (SIRT1) activity, which has anti-inflammatory properties (Hardeland, 2018; Wu et al., 2019).

Additionally, oxidative stress and oxidative-mediated processes including oxygen free radical reaction and lipid peroxidation are the mechanisms causing inflammation (Hardeland, 2019). Numerous cytokines and chemokines secreted by inflammatory cells, such as IL-1, TNF-, and MCP-1, are what cause phagocytic cells to produce reactive oxygen species (ROS) during the start of the inflammation phase (Sánchez et al., 2018). ROS negatively affects neutrophil and macrophage activity and reduces the activation of apoptotic signals (Carrascal et al., 2018).

Numerous innovative perspectives on anti-inflammatory and molecular mechanisms center on the immunological-pineal axis, which mediates the immune system through a negative feedback mechanism (Li et al., 2013). Additionally, these pro-inflammatory cytokines, such as TNF-, IL-1, and IL-6, have several negative consequences on certain tissues, such as the lung, liver, and kidney. These effects include endothelial cell destruction, alterations in vascular permeability, tissue deterioration, and edema (Li et al., 2013; Xie et al., 2020).

2.5.2 Effects of melatonin on the apoptotic mechanism

To preserve the stability of the internal environment, genes control the spontaneous and ordered cell death process known as apoptosis (Li et al., 2013; Calvo et al., 2016). Numerous genes are activated, expressed, and regulated in this process. It is not a manifestation of self-harm occurring under pathological circumstances, but rather a process of death that deliberately seeks out better acclimatization to the living environment (Li et al., 2013; Pandi-Perumal et al., 2018).

Cells exposed to amyloid (A) exhibit several apoptotic features, whereas cells pre-treated with melatonin before exposure to amyloid (A) exhibit a decrease in apoptotic features as a result of decreased intracellular reactive oxygen species (ROS) production, attenuated NF-B activation, and decreased caspase-3 enzyme activity (Li et al., 2013; Pandi-Perumal et al., 2018). Additionally, melatonin reduces NO levels and the apoptosis brought on by an ischemic stroke by increasing the expression of the anti-apoptotic protein BCL-2 in the immortalized pineal gland tumor cell line (Li et al., 2013). Numerous studies have demonstrated that melatonin inhibits the growth of cancerous cells and encourages their apoptosis (Li et al., 2013; Yoo et al., 2020].

2.6 Pregabalin

Pregabalin is an anticonvulsant, analgesic, and anxiolytic drug used to treat epilepsy, neuropathic pain, fibromyalgia, restless leg

syndrome, opioid withdrawal, and generalized anxiety disorder, among other conditions. It is marketed under the trade name Lyrica among others (GAD) (Li et al., 2013; Onakpoya er al., 2019). Additionally, pregabalin possesses antiallodynic qualities. It is utilized in the treatment of partial seizures in epilepsy. It is a gabapentinoid drug that works by blocking specific calcium channels. It lessens discomfort but causes more sedation and visual abnormalities when administered before surgery (Li et al., 2013; Reiter et al., 2018).

In the United States, pregabalin was given the go-ahead for medical use in 2004. It was created to replace the similar drug gabapentin (Li et al., 2013; Saraste and Pulkki, 2020). As of 2019, it is accessible as a generic drug in several nations, including the US (Li et al., 2013; Fine et al., 2020). As of April 2021, a generic version of the extended-release formulation is accessible in the US. It received more than 9 million prescriptions in 2020, ranking it as the 78th most popular drug in the country (Peckham and Sclar, 2018). According to the Prohibited Substances Act of 1970, pregabalin is classified as a Schedule V controlled substance in the US (Martínez et al., 2019).

Headache, wooziness, tiredness, confusion, memory issues, lack of coordination, dry mouth, visual issues, and weight gain are typical adverse effects (Li et al., 2013; Onakpoya et al., 2019). Angioedema, substance abuse, and an increased risk of suicide are examples of serious side effects (Li et al., 2013; Reiter et al., 2018). Addiction may develop when pregabalin is taken at high doses for a long time, but the risk is minimal if taken at recommended doses (Martínez et al., 2019).

2.6.1 Chemistry of pregabalin

Pregabalin is a 3-substituted derivative and -an amino acid that functions as a GABA analog (Martínez et al., 2019). It is specifically (S)-(+)-3-isobutyl-GABA, it shares more structural similarities with the amino acids L-leucine and L-isoleucine than it does with GABA (Han et al., 2022), which may be more significant in terms of its pharmacodynamics [74].

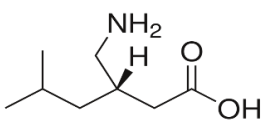

Fig. 3. The chemical structure of pregabalin [70]

2.6.2 Beneficial roles of pregabalin

- •Seizures: Pregabalin is helpful as an adjunctive therapy for drug-resistant focal epilepsy (Uz et al., 2015). It is less effective when used on its own than some other seizure drugs (Li et al., 2013).
- Neuropathic pain: Pregabalin is recommended by the European Federation of Neurological Societies as a first-line treatment for the pain brought on by central neuropathic pain, post-herpetic neuralgia, and diabetic neuropathy (Kugler et al., 2020). A smaller percentage of people benefit significantly, while a larger percentage benefit moderately (Peckham and Sclar, 2018). As a first-line treatment, it is given the same consideration as gabapentin and tricyclic antidepressants, even though the latter are less expensive as of 2010 (Martínez et al., 2019). Pregabalin is typically not seen to be effective in treating severe pain (Henning et al., 2021). No effect on overall pain levels was seen in studies testing the effectiveness of pregabalin for the treatment of acute post-surgical pain, but patients did use less morphine and experienced fewer opioid-related side effects (Henning et al., 2021; Han et al., 2022) Numerous potential pain-relieving strategies have been suggested (Horovitz et al., 2019).
- Anxiety disorders: Pregabalin is a safe medication that can be used to treat generalized anxiety disorder (Li et al., 20134]. Additionally, it lessens preoperative anxiety and is beneficial in the short- and long-term therapy of social anxiety disorder (Li et al., 2013]. However, due to the lack of convincing scientific data supporting pregabalin's efficacy in treating a variety of diseases and its established negative effects, there is worry regarding its off-label use (Li et al., 2013; Horovitz et al., 2019).
- Pregabalin is one of several first-line treatments recommended by the World Federation of Biological Psychiatry for generalized anxiety disorder, although other treatments, such SSRIs, are recommended as first-line treatments for obsessive-compulsive disorder and post-traumatic stress disorder (PTSD) (Li et al., 2013; Montastruc et al., 2018}. Pregabalin

as a complementary therapy for PTSD appears to be successful (Li et al., 2013).

- Generalized anxiety disorder: Pregabalin appears to offer benzodiazepine-like anxiolytic effects with a lower risk of dependence. Pregabalin is comparable to lorazepam, alprazolam, and venlafaxine in terms of effectiveness and starts to take action after a week of use (Saraste and Pulkki, 2020). However, pregabalin has shown superiority by creating more dependable therapeutic effects for psychosomatic anxiety symptoms (Reiter et al., 2018). Long-term studies have demonstrated ongoing efficacy without the emergence of tolerance. In addition, unlike benzodiazepines, it has a positive impact on sleep and sleep architecture, which is defined by the promotion of slow-wave sleep. Compared to benzodiazepines, it results in less severe cognitive and psychomotor impairment (Onakpoya et al., 2019).

2.6.3 The adverse effects of exposure to pregabalin

Pregabalin exposure is linked to euphoria, weight gain, tiredness, weariness, vertigo, leg swelling, abnormal vision, and loss of coordination (Uz et al., 2015). It shares a profile of negative effects with other central nervous system depressants (Li et al., 2013). Pregabalin can paradoxically cause seizures even though it is a depressive and anti-convulsant, especially in severe dosages (Ben-Menachem and Kugler, 2020). The following list of adverse drug reactions is connected to the usage of pregabalin (Fine et al., 2020).

Pregabalin users frequently experience the following side effects, which can range from 1 to 10 percent of the population: blurred vision, diplopia, increased appetite and subsequent weight gain, euphoria, confusion, vivid dreams, changes in libido (increase or decrease), irritability, ataxia, attention changes, feeling high, abnormal coordination, memory impairment, tremors, dysarthria, paresthesia, vertigo, dry mouth and constipation (Montastruc et al., 2018; Onakpoya et al., 2019).

Depression, irritability, agitation, anorgasmia, hallucinations, myoclonus, hypoaesthesia, hyperaesthesia, tachycardia, excessive salivation, hypoglycemia, flushing, rash, muscle cramps, myalgia, arthralgia, urinary incontinence, dysuria, thrombocytopenia, and kidney calculus are uncommon (0.1–1% of those taking pregabalin) (Horowitz et al., 2021).

Neutropenia, first-degree heart blocks, hypotension, hypertension, pancreatitis, dysphagia, oliguria, rhabdomyolysis, and suicidal thoughts or actions are uncommon (0.1% of pregabalin users). There have been cases of recreational use with related negative outcomes (Ben-Menachem and Kugler, 2020).

2.7 Caspase-3 and Apoptosis

2.7.1 Caspase-3

The caspase family (CED-3) is a protein family with strong similarity to the C. elegans cell death abnormal-3 gene (Xu et al., 2023). Caspases can be further broken down into inflammatory caspases, initiator caspases (caspase-2, -8, -9, and -10), and executioner caspases (caspase-3, -6, and -7); (Caspase-1, -4, -5, -11) (Qi et al., 2020). Caspase-3 operates by catalyzing the C-terminal cysteine residue to preferentially lyse the peptide bond after aspartic acid residues. Caspase-3 occurs as an inactive proenzyme in the cytoplasm. Granzyme B or caspase-10 cleaved caspase-3 at the D175 location. Then, p20 and p11 subunits were assembled, activating caspase-3 in the process. Neither autocatalysis nor self-splicing could activate caspase-3 (Xu et al., 2023).

Activated caspase-3 can cause cell death by destroying intracellular structural and functional proteins (Qi et al., 2020). Caspase-3 is toward the end of the caspase cascade and is triggered by both the intrinsic and extrinsic death pathways in apoptosis, in contrast to other members of the caspase family (Lossi et al., 2018). In comparison to other enzymes, caspase-3 is known to have a variety of effects on the mechanism of tumor cell death. Because many researchers have used caspase-3 as a starting point in recent years to understand the mechanism of tumor cell death, apoptosis resistance, and pyroptotic tumor suppressor, the research on caspase-3 dependent cell death is described below (Jiang et al., 2020).

2.7.2 Caspase-3-dependent cell death pattern Apoptosis

The apoptotic caspases are activated during apoptosis, a non-inflammatory form of programmed cell death that can take place either

by an intrinsic or an extrinsic pathway (Qi et al., 2020). Mitochondrial damage triggers the intrinsic pathway. After the mitochondrion releases cytochrome C into the cytoplasm, Apaf-1, a caspase-9 precursor, and other components combine to form an apoptosome, which then triggers caspase-9 (Lossi, 2022).

After cleaving and activating pro-caspase-3/7, activated caspase-9 proceeds to kill cells by cleaving a variety of cellular endogenous substrates. Signals from cell surface death receptors, such as tumor necrosis factor (TNF), bind to these receptors, causing them to oligomerize, which attracts and activates caspase-8, which subsequently recruits and activates pro-caspase-3 to cause apoptosis (Lossi et al., 2018; Unnisa et al., 2022). Eventually, activated caspase-3 is thought to be a critical protein for apoptosis. It is found at the end of the caspase cascades and is triggered by both endogenous and external apoptotic routes [78].

When caspase-3 is activated, the plasma membrane blebs, chromatin condenses, DNA is broken down, and phosphatidylserine is exposed on the extracellular side of the plasma membrane (Qi et al., 2020; Lossi, 2022). The morphological and biochemical traits of apoptotic cells were thus created. Many chemotherapeutic drugs used to treat cancer are hypothesized to have lethal effects on tumor cells through inducing apoptosis. Apoptosis may be prevented, however, by inhibitors' lack of caspase function as well as by caspase alterations and mutations in cell signaling pathways (Yao et al., 2019).

3. CONCLUSION

Pregabalin and melatonin have immense therapeutic potential in several physiological and clinical applications. Melatonin plays an important role in maintaining normal biological functions, especially anti-inflammatory responses and sleep, due to its neuroprotective properties, antioxidant activities, and control of circadian rhythms.

On the other hand, pregabalin is an anticonvulsant and analgesic drug that is especially indicated for anxiety disorders, epilepsy, and neuropathic pain. Due to its ability to affect calcium channels, it has become an essential drug in pain treatment and management and seizure management. Whereas great potential has been evident in the treatment of neurological disorders with such substances, further study is needed to understand their long-term impacts completely, especially in diverse settings in clinics and populations [80]. Despite melatonin showing promise in neuroprotection and control of circadian rhythms, further research on its immunomodulatory and anti-cancer effects could extend its therapeutic applications. The potential adverse effect of pregabalin, especially after long-term treatment, must also be taken into consideration in the careful weighing of a balance between the safety and efficacy of drugs for patients.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

I hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.) and text-to-image generators have been used during the writing or editing of this manuscript.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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