JOURNAL OF PHARMA INSIGHTS AND RESEARCH

REVIEW ARTICLE

Role of Melatonin Receptors as Regulators of Neurophysiology and Therapeutic Targets

Imran Rashid*, Mashooq Ah Mir, Aaliya Andleeb, Abhishek Kumar, Umehear Munshi, Danish Habib, Subzar Ahmad

UG Scholar, College of Pharmacy, B Pharmacy, RIMT University, Gobindgarh, Punjab, India

Publication history: Received on 29th March; Revised on 4th April; Accepted on 12th April

Article DOI: 10.5281/zenodo.11200118

Abstract: Melatonin receptors, primarily MT1 and MT2 subtypes, have emerged as critical regulators of diverse neurophysiological processes and promising therapeutic targets. These G protein-coupled receptors play a pivotal role in modulating circadian rhythms, sleep-wake cycles, neurotransmission, synaptic plasticity, and neuroprotection. Their activation triggers intricate signaling cascades, including cAMP, cGMP, and calcium pathways, while exhibiting crosstalk with MAPK and PI3K/Akt pathways. Moreover, melatonin receptors influence cognitive function, memory, and emotional regulation, underscoring their potential in neuropsychiatric disorders like depression, anxiety, and schizophrenia. Pharmacological targeting of these receptors has gained significant traction, with the development of selective ligands and investigative tools to enhance therapeutic efficacy. Notable applications include managing sleep disorders, pain, cancer, and neurodegenerative diseases. Furthermore, melatonin receptor agonists have shown promising results in preclinical studies for treating mood disorders and improving cognitive performance. Despite the challenges, ongoing research efforts aim to elucidate the molecular mechanisms, receptor heterodimers, and allosteric modulation, paving the way for innovative therapeutic strategies leveraging the multifaceted roles of melatonin receptors.

Keywords: Melatonin; Receptors; Circadian rhythms; Neuroprotection; Cognitive function; Therapeutic targets.

1. Introduction

Melatonin, a multifaceted hormone primarily synthesized by the pineal gland, has garnered significant attention for its diverse physiological roles and therapeutic potential. At the forefront of melatonin's actions are its receptors, MT1 and MT2, which belong to the G protein-coupled receptor (GPCR) superfamily. [1] These receptors serve as critical mediators of melatonin's effects on various bodily processes, including circadian rhythms, sleep regulation, neuronal function, and cognitive performance. The circadian regulation of numerous physiological and behavioral processes is a fundamental function governed by the melatonin receptors. Expressed in the suprachiasmatic nucleus (SCN) of the hypothalamus, these receptors play a pivotal role in synchronizing the body's internal clock with external light-dark cycles. Melatonin receptor activation modulates the firing patterns of SCN neurons, ultimately influencing the secretion of hormones and neurochemicals responsible for coordinating sleep-wake cycles, body temperature, and metabolic processes. [2,3]

Beyond their role in circadian regulation, melatonin receptors have gained significant attention due to their involvement in neurological processes and potential therapeutic applications. Within the central nervous system (CNS), these receptors are widely distributed in various brain regions, including the hippocampus, cortex, and cerebellum. [4,5] Their activation exerts profound effects on neurotransmission, synaptic plasticity, and neuronal survival, making them attractive targets for addressing neuropsychiatric disorders and neurodegenerative diseases. [6] Melatonin receptors modulate neurotransmitter release and signaling, influencing the activity of neurotransmitters such as glutamate, gamma-aminobutyric acid (GABA), dopamine, and serotonin. This regulation has implications for cognitive processes, emotional regulation, and neuropsychiatric conditions like depression, anxiety, and schizophrenia. [7] Furthermore, melatonin receptor activation has been implicated in enhancing synaptic plasticity, a critical process underlying learning and memory formation, highlighting their potential in cognitive enhancement and counteracting age-related cognitive decline.

Notably, melatonin receptors exert neuroprotective effects through various mechanisms, including reducing oxidative stress, modulating apoptotic pathways, and promoting neuronal survival. [8] These properties have sparked interest in exploring melatonin receptor agonists as potential therapeutic agents for neurodegenerative disorders, such as Alzheimer's disease, Parkinson's disease, and stroke.

* Corresponding author: Imran Rashid

The therapeutic potential of melatonin receptors extends beyond the CNS, encompassing applications in pain management, cancer treatment, and metabolic disorders. [9, 10] Melatonin receptor activation has been shown to exhibit analgesic properties, particularly through the MT2 subtype, offering promising avenues for novel pain-relieving therapies. Additionally, melatonin receptors play a role in regulating cellular proliferation and apoptosis, making them attractive targets for developing anticancer agents. Despite the wealth of knowledge surrounding melatonin receptors, numerous challenges and unanswered questions remain. [11-14] Elucidating the intricate signaling pathways, receptor dimerization patterns, and allosteric modulation mechanisms is crucial for developing more selective and potent therapeutic agents. Additionally, understanding the interplay between melatonin receptors and other physiological systems, such as the immune and endocrine systems, may uncover novel therapeutic avenues. The objective of this review is to provide a comprehensive and up-to-date analysis of the multifaceted roles of melatonin receptors in neurophysiology, their therapeutic potential across various disorders, and the challenges and future directions in melatonin receptor research.

2. Classification and distribution of melatonin receptors

Melatonin receptors are widely expressed throughout various tissues and organs, reflecting their diverse physiological roles. The classification and distribution of these receptors have been extensively studied, providing insights into their functional significance and therapeutic potential [15-17].

2.1. Classification of Melatonin Receptors

Melatonin receptors are classified into three main subtypes: MT1 (encoded by the MTNR1A gene), MT2 (encoded by the MTNR1B gene), and MT3 (also known as the enzyme quinone reductase 2). The MT1 and MT2 receptors belong to the G protein-coupled receptor (GPCR) superfamily and are the primary targets for melatonin signaling [18]. These receptors exhibit distinct pharmacological profiles, tissue distribution patterns, and functional roles.

2.1.1. MT1 Receptors

The MT1 receptors are widely distributed throughout the body, with high expression levels observed in the brain, particularly in the suprachiasmatic nucleus (SCN) of the hypothalamus, the pituitary gland, and the retina [19, 20]. Additionally, MT1 receptors are found in various peripheral tissues, including the cardiovascular system, reproductive organs, immune cells, and adipose tissue. These receptors play crucial roles in regulating circadian rhythms, reproductive functions, immune responses, and metabolic processes [21].

2.1.2. MT2 Receptors

MT2 receptors are predominantly expressed in the brain, particularly in regions associated with visual processing, such as the retina and the suprachiasmatic nucleus. They are also found in other areas of the central nervous system, including the hippocampus, cortex, and cerebellum. [22, 23] Additionally, MT2 receptors are present in peripheral tissues, including the cardiovascular system, reproductive organs, and immune cells. [24] These receptors are implicated in the modulation of sleep-wake cycles, visual processing, and various physiological processes, such as cardiovascular function and immune regulation.

2.1.3. MT3 Receptors

The MT3 receptor, initially identified as a melatonin-binding site, is now recognized as the enzyme quinone reductase 2 (QR2). [25] This enzyme is involved in the detoxification of quinones and the scavenging of reactive oxygen species, contributing to the antioxidant properties of melatonin. [26] The MT3 receptor is widely distributed in various tissues, including the brain, liver, kidney, and adipose tissue.

2.2. Distribution of Melatonin Receptors in the Brain

The distribution of melatonin receptors in the brain is of particular interest due to their involvement in neurological processes and potential therapeutic applications. [27] The MT1 and MT2 receptors are widely expressed in various brain regions, including:

2.2.1. Suprachiasmatic Nucleus (SCN)

MT1 and MT2 receptors are highly expressed in the SCN, the central pacemaker that regulates circadian rhythms and sleep-wake cycles. [28]

2.2.2. Hippocampus

Both MT1 and MT2 receptors are present in the hippocampus, a brain region crucial for learning, memory, and spatial navigation.[29]

2.2.3. Cortex

Melatonin receptors are found in various cortical areas, including the prefrontal cortex, which is involved in cognitive functions and emotional regulation. [30]

2.2.4. Cerebellum

MT1 and MT2 receptors are expressed in the cerebellum, a brain structure associated with motor coordination and cognitive processes. [31]

2.2.5. Retina

The retina is a major site for MT2 receptor expression, playing a role in visual processing and circadian entrainment. [32]

2.2.6. Hypothalamus

In addition to the SCN, melatonin receptors are present in other hypothalamic regions, contributing to the regulation of various neuroendocrine functions. [33]

2.2.7. Brainstem

Melatonin receptors are found in various brainstem nuclei, such as the locus coeruleus and the raphe nuclei, which are involved in arousal, sleep, and mood regulation [34]

Table 1. Distribution of Melatonin Receptors in Various Brain Regions

Brain Region	MT1 Receptor	MT2 Receptor	Functions
Suprachiasmatic Nucleus (SCN)	✓	✓	Circadian rhythm regulation, sleep-wake cycles
Hippocampus	✓	✓	Learning, memory, spatial navigation
Prefrontal Cortex	✓	✓	Cognitive functions, emotional regulation
Cerebellum	✓	✓	Motor coordination, cognitive processes
Retina	✗	✓	Visual processing, circadian entrainment
Hypothalamus	✓	✓	Neuroendocrine regulation
Brainstem (e.g., locus coeruleus, raphe nuclei)	✓	✓	Arousal, sleep, mood regulation

3. Molecular mechanisms of melatonin receptor signaling

3.1. G-protein-coupled receptor (GPCR) signaling pathways

A vast family of membrane receptors known as G-protein-coupled receptors (GPCRs) is essential to cellular signaling. They impact multiple physiological processes by activating diverse signaling pathways in response to a broad range of environmental cues. Studies on the physiological significance of beta-cell G protein signaling pathways in vivo, which use mutant M3 muscarinic acetylcholine receptors to activate various classes of G proteins, demonstrate the wide-ranging influence of GPCRs [35]. by phosphorylating GPCRs and sequestering Gαq/11 proteins, G Protein-coupled Receptor Kinase 2 (GRK2) has been found to be a strong regulator of Gq/11 signaling, underscoring the intricacy of GPCR regulation.[36]

GPCRs play a complex function in cell signaling and regulation. Agonist activation of GPCRs starts various important processes, such as feedback desensitization, internalization of GPCRs, and coupling to heterotrimeric G protein-independent pathways. [37] by spatially restricting RGS activity to the active GPCR, compartmentalization of Regulator of G Protein Signaling (RGS) activity has been proposed as a unique strategy for controlling GPCR signaling pathways.[38] The transducer-specific molecular efficacies of ligands for the AT1R receptor have been measured in vitro using a cell-free method utilizing GPCR-transducer fusion proteins. This work has provided insight into the molecular causes of biased agonism and shown the possibility of creating ligands that preferentially activate particular signaling pathways. [39] a thorough analysis emphasized the functions of important GPCR signaling effectors in pharmacology by highlighting their involvement in controlling intracellular signaling, including heterotrimeric G proteins, GPCR kinases (GRKs), and β-arrestins.[40] All of these investigations highlight the importance of

GPCRs and the signaling pathways they are linked to in the operation of cells. Numerous parts and processes are involved in the complex control of GPCR signaling pathways, which enables a wide variety of cellular reactions to outside stimuli.

3.2. Activation of downstream effectors: cAMP, cGMP, calcium signaling

In many physiological processes and cellular reactions, the activation of downstream effectors like cyclic AMP (cAMP), cyclic GMP (cGMP), and calcium signaling is essential. The complex interactions between these signaling channels and how they affect cellular processes have been studied. The level of intracellular calcium plays a crucial role in regulating multiple cellular processes by exerting a major influence on the production of cAMP in response to hormones. In cultured rat inner medullary collecting tubule cells stimulated by arginine vasopressin (AVP), for example, changes in intracellular calcium have been demonstrated to significantly alter cAMP generation. This suggests that calcium plays a crucial role in cAMP-mediated processes, independent of prostaglandin E2 synthesis.[41] calcium ionophore A23187 stimulates ISO- and VIP-stimulated cAMP synthesis in the chick embryo ciliary epithelium, indicating the function of calcium in regulating cAMP levels in response to various stimulants.[48] The intricate interplay between the calcium and cAMP signaling pathways has been well-documented, with a focus on interactions that take place in specific cell domains. [42]

It has also been discovered that certain hormones, such as vasoactive intestinal peptide, corticotropin (ACTH)-releasing factor, and catecholamines, enhance cytosolic calcium in AtT-20 cells by inducing ACTH secretion and cAMP synthesis, demonstrating the intimate connection between the cAMP and calcium pathways.[43] According to a study, the cAMP signal that tastants cause in taste buds is not affected by calcium, indicating that cAMP and calcium have different downstream signaling pathways that are activated in response to taste receptor activation. Furthermore, cAMP-dependent protein kinase can control local Ca2+ release, changing IP3 receptor characteristics and enabling selective calcium release in response to various external stimuli. This allows for the specificity of calcium signaling.[44] These results highlight the vital roles that cAMP, cGMP, and calcium signaling pathways play in cellular signaling and offer insight into possible therapeutic targets for modifying these pathways. They also demonstrate the dynamic and intricate connections between these networks.

3.3. Crosstalk with other signaling pathways: MAPK, PI3K/Akt, etc.

The complex interplay among signaling pathways, such as PI3K/Akt and MAPK, is essential for several biological processes, such as the osteogenesis of periodontal ligament stem cells, chemotaxis of breast cancer cells, and tumor microenvironments. Diverse studies have demonstrated distinct aspects of this crosstalk:

- Regulatory T cells' migration and proliferation are influenced by the interplay between the MAPK/P27 and CBM complex/NF-ϰB signaling pathways, which in turn affects the tumor microenvironment.[45]
- The ERK and Akt signaling pathways interact with the MAPK and PI3K/Akt signaling pathways in the setting of breast cancer cell chemotaxis, which contributes to the heterogeneity of cell chemotaxis.[46]
- There is growing evidence that interleukin-1β has a "double-edged sword" effect on the osteogenesis of periodontal ligament stem cells by stimulating the BMP/Smad pathway at lower dosages and activating the NF-ϰB and MAPK signaling pathways at larger doses.[46]
- Studies on pancreatic cancer have shown that the p38 stress-associated MAPK α pathway is essential for controlling PDAC tumor cells' generation of IL-1α and influencing inflammatory tumor-stromal interaction.[46]
- The intricacy of signaling pathway interactions is highlighted by the discovery of the RAF-1/MST-2 interaction as a novel link indicating crosstalk between the MAPK and Hippo signaling pathways in malignant melanoma.[46]
- The study of circular RNAs in colorectal cancer has further shed light on how these RNA molecules interact with multiple signaling pathways, including MAPK and PI3K/Akt, affecting tumor cell proliferation, invasion, migration, and apoptosis. [47]

These studies highlight the intricate and multifaceted nature of the crosstalk between various signaling pathways, including MAPK and PI3K/Akt, highlighting their critical roles in diverse biological and pathological processes. [48] Furthermore, it was discovered that CNKSR1 regulates MAPK inhibition responsiveness in pancreas cancer through crosstalk with AKT signaling, highlighting its potential as a molecular marker for precision medicine targeting MEK and AKT pathways.

4. Regulation of neurotransmission by melatonin receptors

Melatonin receptors exert a profound influence on neurotransmission, modulating the release and signaling of various neurotransmitters crucial for proper brain function. This intricate regulatory mechanism has garnered significant attention due to its implications in neurological processes, cognitive function, and the development of potential therapeutic interventions.

4.1. Modulation of Neurotransmitter Release

Melatonin receptors play a pivotal role in regulating the release of several neurotransmitters, including glutamate, gamma-aminobutyric acid (GABA), dopamine, and serotonin. These neurotransmitters are fundamental for proper neuronal communication, synaptic plasticity, and cognitive processes. [49]

4.1.1. Glutamate

Melatonin receptors have been shown to modulate glutamate release, a major excitatory neurotransmitter in the brain. By interacting with presynaptic proteins and voltage-gated calcium channels, melatonin receptors can influence glutamate release, potentially impacting synaptic transmission and neuronal excitability.

4.1.2. GABA

Melatonin receptors can regulate the release of GABA, the primary inhibitory neurotransmitter in the brain. This regulation is believed to contribute to melatonin's potential anxiolytic and anticonvulsant effects, as well as its role in modulating sleep and circadian rhythms.

4.1.3. Dopamine

Melatonin receptors have been implicated in the modulation of dopaminergic neurotransmission, particularly in brain regions associated with motor control, reward processing, and cognition. This interaction has implications for conditions like Parkinson's disease and schizophrenia, where dopamine dysregulation plays a crucial role.

4.1.4. Serotonin

The crosstalk between melatonin receptors and serotonin receptors, such as the 5-HT2A receptor, has been extensively studied. This interaction may underlie the potential antidepressant and anxiolytic effects of melatonin, as well as its impact on sleep, mood, and cognition.

4.2. Influence on Synaptic Plasticity and Neuronal Excitability

Melatonin receptors have a profound influence on synaptic plasticity, a fundamental process underlying learning, memory formation, and cognitive function.[50] By modulating neurotransmitter release and signaling, melatonin receptors can affect synaptic strength, neuronal excitability, and the overall activity of neural circuits.

Melatonin receptor activation has been associated with changes in long-term potentiation (LTP) and long-term depression (LTD), two key mechanisms involved in synaptic plasticity. These effects may contribute to melatonin's potential cognitive-enhancing properties and its role in counteracting age-related cognitive decline.[51]

Furthermore, melatonin receptors can influence neuronal excitability by modulating the activity of ion channels, neurotransmitter receptors, and intracellular signaling pathways. This regulation has implications for conditions characterized by abnormal neuronal excitability, such as epilepsy, neuropathic pain, and certain neurodegenerative disorders.

4.2.1. Neuroprotective Effects

In addition to their regulatory roles in neurotransmission and synaptic plasticity, melatonin receptors have been implicated in neuroprotective mechanisms. By modulating neurotransmitter release and signaling, melatonin receptors can potentially mitigate excitotoxicity, oxidative stress, and apoptotic processes, thereby promoting neuronal survival. [52]

Melatonin receptor activation has been shown to attenuate the delayed degeneration of hippocampal neurons caused by increased excitatory neurotransmission and the nitridergic pathway. This neuroprotective effect may have therapeutic implications for conditions such as ischemic stroke, traumatic brain injury, and neurodegenerative diseases.

5. Behavioral effects of melatonin receptor activation

Melatonin receptor activation exerts a profound influence on various behavioral processes, ranging from circadian rhythms and sleep-wake cycles to cognitive function, emotional regulation, and neuroprotection. These effects have garnered significant attention due to their potential therapeutic applications in neurological disorders, psychiatric conditions, and age-related cognitive decline. [53]

5.1. Regulation of Circadian Rhythms and Sleep-Wake Cycles

The regulation of circadian rhythms and sleep-wake cycles is one of the most well-established functions of melatonin receptor activation. Melatonin receptors, particularly MT1 and MT2, are highly expressed in the suprachiasmatic nucleus (SCN) of the hypothalamus, which acts as the central pacemaker for the body's circadian clock. Activation of melatonin receptors in the SCN modulates the firing patterns of neurons, influencing the release of various hormones and neurotransmitters that regulate sleep-wake cycles, body temperature, and metabolic processes. Disruptions in melatonin receptor signaling can lead to circadian rhythm disorders, insomnia, and other sleep-related disturbances. Melatonin receptor agonists, such as ramelteon and tasimelteon, have been approved for the treatment of sleep disorders, demonstrating the therapeutic potential of targeting these receptors in regulating sleep and circadian rhythms.[54]

5.2. Effects on Cognitive Function and Memory

Melatonin receptor activation has been implicated in modulating cognitive function and memory processes. By influencing neurotransmission, synaptic plasticity, and neuronal survival, melatonin receptors play a crucial role in maintaining cognitive health and counteracting age-related cognitive decline. Preclinical studies have shown that melatonin receptor activation can enhance cognitive performance and memory formation in animal models of chronic cerebral hypoperfusion, Alzheimer's disease, and other neurodegenerative conditions. These effects are mediated through various mechanisms, including the modulation of hippocampal signaling pathways, reduction of oxidative stress, and promotion of neuronal survival. [55]

Additionally, melatonin receptor activation has been associated with improved learning and memory in sleep-deprived individuals, suggesting its potential therapeutic application in addressing cognitive deficits related to sleep disturbances.

5.3. Emotional Regulation and Neuropsychiatric Disorders

Melatonin receptor activation has been implicated in the regulation of emotional states, mood, and behavior, with potential implications for neuropsychiatric disorders such as depression, anxiety, and schizophrenia. Preclinical studies have demonstrated that melatonin receptor agonists can exhibit antidepressant and anxiolytic effects, potentially through their interactions with neurotransmitter systems like serotonin, dopamine, and GABA. Additionally, melatonin receptor activation has been shown to modulate inflammatory pathways and oxidative stress, which are implicated in the pathophysiology of various neuropsychiatric disorders.[56] Furthermore, melatonin receptor activation has been associated with the regulation of social behavior and emotional processing, suggesting its potential therapeutic applications in conditions like autism spectrum disorders and social anxiety disorders.

5.4. Neuroprotective Effects

Melatonin receptor activation has been extensively studied for its neuroprotective properties, which may have implications for various neurological disorders and neurodegenerative conditions. Melatonin receptor activation has been shown to attenuate excitotoxicity, oxidative stress, and neuroinflammation, all of which are major contributors to neuronal damage and dysfunction. By modulating these pathways, melatonin receptors can potentially prevent or mitigate neuronal death and promote neuronal survival. Preclinical studies have demonstrated the neuroprotective effects of melatonin receptor activation in animal models of ischemic stroke, traumatic brain injury, Alzheimer's disease, and Parkinson's disease. These findings suggest the potential therapeutic utility of melatonin receptor agonists in preventing or slowing the progression of neurodegenerative diseases. [2, 11]

The behavioral effects of melatonin receptor activation are multifaceted and span various domains, including circadian regulation, cognitive function, emotional regulation, and neuroprotection. Further research is warranted to elucidate the specific mechanisms underlying these effects and to develop targeted therapeutic interventions leveraging the activation of melatonin receptors for the treatment of neurological and psychiatric disorders.

6. Clinical implications and therapeutic potential

The multifaceted roles of melatonin receptors in regulating various physiological processes and their impact on neurological and behavioral functions have opened up exciting avenues for therapeutic exploration. As our understanding of these receptors continues to deepen, their clinical implications and potential as drug targets are becoming increasingly apparent.

6.1. Sleep Disorders and Circadian Rhythm Dysregulation

One of the most well-established clinical applications of melatonin receptor targeting is in the treatment of sleep disorders and circadian rhythm disturbances. Melatonin receptor agonists, such as ramelteon and tasimelteon, have been approved for the treatment of insomnia and circadian rhythm sleep-wake disorders, respectively. These medications work by selectively activating melatonin receptors, thereby regulating sleep-wake cycles and promoting sleep onset and maintenance. [11, 32]

6.2. Neuropsychiatric Disorders

Melatonin receptor modulation has shown promising potential in the management of various neuropsychiatric disorders, including depression, anxiety, and schizophrenia. Preclinical studies have demonstrated the antidepressant and anxiolytic effects of melatonin receptor agonists, potentially mediated through their interactions with neurotransmitter systems and their ability to modulate oxidative stress and neuroinflammation. Additionally, melatonin receptor agonists have been explored as adjunctive treatments in schizophrenia, where they may help alleviate sleep disturbances and potentially improve cognitive function and negative symptoms. [12, 14]

6.3. Neurodegenerative Diseases

The neuroprotective properties of melatonin receptor activation have sparked interest in their potential therapeutic applications in neurodegenerative disorders. Preclinical studies have demonstrated the ability of melatonin receptor agonists to attenuate oxidative stress, neuroinflammation, and neuronal death in animal models of Alzheimer's disease, Parkinson's disease, and stroke. Moreover, melatonin receptor activation has been shown to modulate synaptic plasticity and cognitive function, suggesting its potential in slowing cognitive decline and improving functional outcomes in neurodegenerative diseases. [3, 9, 10]

6.4. Pain Management

Emerging evidence suggests that melatonin receptor activation, particularly through the MT2 subtype, may have analgesic properties. Preclinical studies have demonstrated the potential of melatonin receptor agonists in alleviating various types of pain, including neuropathic, inflammatory, and chronic pain. This has opened up avenues for the development of novel pain management strategies targeting melatonin receptors. [12]

6.5. Cancer Therapy

Melatonin receptors have been implicated in the regulation of cellular proliferation, apoptosis, and angiogenesis, making them attractive targets for cancer therapy. Preclinical studies have shown that melatonin receptor agonists can inhibit tumor growth and metastasis in various cancer types, including breast, prostate, and colon cancer. Additionally, melatonin receptor activation has been explored as an adjuvant therapy to enhance the efficacy of existing cancer treatments, such as chemotherapy and radiation therapy. Despite the promising potential of melatonin receptor targeting, several challenges remain. These include the development of more selective and potent agonists or antagonists, elucidating the complex signaling pathways and receptor interactions, and addressing potential side effects or adverse reactions. [24, 33]

Table 2. Therapeutic Potential of Melatonin Receptor Targeting

Condition/Disease	Potential Therapeutic Approach
Sleep Disorders and Circadian Rhythm Dysregulation	Melatonin receptor agonists (e.g., ramelteon, tasimelteon) for regulating sleep-wake cycles
Depression and Anxiety	Melatonin receptor agonists for antidepressant and anxiolytic effects
Schizophrenia	Melatonin receptor agonists as adjunctive treatment for sleep disturbances, cognitive deficits
Neurodegenerative Diseases (e.g., Alzheimer's, Parkinson's)	Melatonin receptor agonists for neuroprotection, cognitive enhancement
Pain Management	Melatonin receptor agonists, particularly MT2 agonists, for analgesic effects
Cancer	Melatonin receptor agonists for inhibiting tumor growth, metastasis, and enhancing existing treatments

7. Conclusion

The multifaceted roles of melatonin receptors in regulating various physiological processes, particularly in the nervous system, have positioned them as promising therapeutic targets for a wide range of clinical conditions. From sleep disorders and neuropsychiatric disorders to neurodegenerative diseases, pain management, and cancer therapy, the activation or modulation of melatonin receptors offers exciting avenues for therapeutic intervention. As research continues to unravel the intricate mechanisms underlying melatonin receptor function and signaling, the development of novel and targeted therapies leveraging these receptors holds great promise for improving patient outcomes and overall well-being

References

[1] R. Ader, ed., (1981) Psychoneuroimmunology. Academic Press, New York .

[2] Angeli, A., G. Gatti, M.L. Sartori, D. Del Ponte, R. Cerignola (1988) Effect of exogenous melatonin on human natural killer (NK) cell activity. An approach to the immunomodulatory role of the pineal gland. In: The pineal gland and cancer. D. Gupta, A. Attanasio, R.J. Reiter, eds. Müller and Bass, Tubingen , pp. 145–157.

[3] Barath, P., G. Csaba (1974) Histological changes in the lung, thymus and adrenal one and a half year after pinealectomy. Acta Biol. Acad. Sci. Hung. 25: 123–125.

[4] Fraschini, F., F. Scaglione, G. Demartini, V. Lucini, P. Sacerdote (1990) Melatonin action on immune responses. In: Advances in Pineal Research 4. R.J. Reiter, A. Lukaszyk, eds. John Libbey, London , pp. 225–233.

[5] Giordano, M., M.S. Palermo (1991) Melatonin-induced enhancement of antibody dependent cellular cytotoxicity. J. Pin. Res. 10: 117–121.

[6] Maestroni, G.J.M., A. Conti (1990) The pineal neurohormone melatonin stimulates activated CD4+, Thy-1+ cells to release opioid agonist(s) with immunoenhancing and anti-stress properties. J. Neuroimmunol. 28: 167–176.

[7] Becker, J., G. Veit, R. Handgretinger, A. Attanasio, G. Bruchett, I. Trenner, D. Niethammer, D. Gupta (1988) Circadian variations in the immunomodulatory role of the pineal gland. Neuroendocrinol. Lett. 10: 65–80.

[8] Bernton, E.W., H.U. Bryant, J.W. Holaday (1991) Prolactin and immune function. In: Psychoneuroimmunology II. R. Ader, D.L. Felten, N. Cohen, eds. Academic Press, San Diego , pp. 403–429.

[9] Hansson, I., R. Holmdahl, R. Mattsson (1992) The pineal hormone melatonin exaggerates development of collagen-induced arthritis in mice. J. Neuroimmunol. 39: 23–31.

[10] Jankovic, B.D., K. Isakovic, S. Petrovic (1970) Effect of pinealectomy on immune reactions in the rat. Immunology 8: 1–6.

[11] Kelley, K.W. (1991) Growth hormone in immunobiology. In: Psychoneuroimmunology II. R. Ader, D.L. Felten, N. Cohen, eds. Academic Press, San Diego , pp. 377–403.

[12] Kumar, M.S.A., D.L. Chen, D.C. Sharp, J.M. Liv, P.S. Kalra, S.P. Kalra (1982) Diurnal fluctuation in methionine enkephalin levels in the hypothalamus and preoptic area of the male rat: effect of pinealectomy. Neuroendocrinology 35: 28–34.

[13] Martelletti, P., G. Stirparo, L. de Stefano, E. Bonmassar, M. Giacovazzo, C. Rinaldi-Garaci (1987) Reduced activity of the NK cells from patients with cluster headache and the "in vitro" response to β-interferon. Headache 27: 548–552.

[14] Reiter, R.J. (1991) Melatonin: The chemical expression of darkness. Mol. Cell. Endocrinol. 79: C153–C158.

[15] Maestroni, G.J.M., A. Conti, W. Pierpaoli (1988b) Role of the pineal gland in immunity. III. Melatonin antagonizes the immunosuppressive effect of acute stress via an opiatergic mechanism. Immunology 63: 465–469.

[16] Besedovsky, H.O., A.E. Delrey, E. Sorkin, A. Dinarello (1986) Immunoregulatory feedback between interleukin-1 and glucocorticoid hormones. Science 233: 652–654.

[17] Bindoni, M., A. Cambria (1968) Effects of pinealectomy on the in vivo and in vitro biosynthesis of nucleic acids and on the mitotic rate in some organs of the rat. Arch. Sci. Biol. 52: 271–283.

[18] Lakin, M.L., C.H. Miller, M.L. Stott, D.W. Winters (1981) Involvement of the pineal gland and melatonin in murine analgesia. Life Sci. 19: 2543–2547.

[19] Lewinski, A., P. Zelazowsky, E. Sewerynek, G. Zerek-Melen, M. Szkudlinski (1989) Melatonin-induced immuno-suppression of human lymphocyte natural killer activity in vitro. J. Pineal Res. 7: 153–164.

[20] Lewis, T. (1974) Biological signal for self identification. In: Progress in Immunology II. N. Brent, J. Helborow, eds. North Holland Publishing Company, Amsterdam , Vol 2, pp. 239–247.

[21] Lissoni, P., S. Barni, G. Tancini, S. Crispino, F. Paolor-Ossi, V. Lucini, M. Mariani, G. Cattaneo, D. Esposti, G. Esposti, F. Fraschini (1987) Clinical study of melatonin in untreatable advanced cancer patients. Tumori 73: 475–480.

[22] Muscettola, M., G. Grasso, G. Fanetti, C. Tanganelli, C. Borghesi-Nicoletti (1992) Melatonin and modulation of interferon-gamma production. Neuropeptides 22: 46 (Abstract).

[23] Maestroni, G.J.M., A. Conti (1989) Beta-endorphin and dynorphin mimic the circadian immunoenhancing and anti-stress effects of melatonin. Int. J. Immunopharmacol. 11: 333–340.

[24] Bittman, E.L. (1992) A durational signal regulating steroid-dependent and -independent aspects of limbic and hypophyseal function. Melatonin and the Pineal Gland. From Basic Science to Clinical Application, Satellite Symposium of the 19th International Congress of Endocrinology, Paris, (abstract).

[25] Blask, D.E. (1984) The pineal: an oncostatic gland? In: The Pineal Gland. R.J. Reiter, ed. Raven Press, New York , pp. 253–285.

[26] Lissoni, P., F. Morabito, G. Esposti, D. Esposti, G. Ripamonti, F. Fraschini (1988) A study on the thymuspineal axis: interactions between thymic hormones and melatonin secretion. Acta Med. Auxol. 20: 35–39.

[27] Lissoni, P., S. Barni, C. Archili, G. Cattaneo, F. Rovelli, A. Conti, G.J.M. Maestroni, G. Tancini (1990) Endocrine effects of a 24-hour intravenous infusion of interleukin-2 in the immunotherapy of cancer. Anticancer Res. 10: 753–758.

[28] Sarella PN, Dadishetti JP, Asogwa PO, Kakarparthy R. Pharmacological and Non-pharmacological Management of Bipolar Disorder with Comorbid Huntington's Disease: A Case Report. Journal of Clinical and Pharmaceutical Research. 2023 Apr 30:5-8.

[29] Ortaldo, J.R., R.B. Heberman (1984) Heterogeneity of natural killer cells. Annu. Rev. Immunol. 2: 359–377.

[30] Rella, W., V. Lapin (1976) Immunocompetence of pinealectomized and simultaneously pinealectomized and thymectomized rats. Oncology 33: 3–6.

[31] Sarella PN, Thammana PK. Potential applications of Folate-conjugated Chitosan Nanoparticles for Targeted delivery of Anticancer drugs. Research Journal of Pharmaceutical Dosage Forms and Technology. 2023 Oct 1;15(4):281-8.

[32] Champney, T.H., D.N. McMurray (1991) Spleen morphology and lymphoproliferative activity in short photoperiod exposed hamsters, In: Role of melatonin and pineal peptides in neuroimmunomodulation. F. Fraschini, R.J. Reiter, eds. Plenum Pub. Co., London , pp. 219–225.

[33] Pang, S.F., E. Yuan, Z.H. Yu, X.L. Wang, P.L. Tang, P.P.N. Lee, M.Y.C. Yau (1991) Melatonin binding sites in the brain and spleen. In: Role of melatonin and pineal peptides in neuroimmunomodulation. F. Fraschini, R.J. Reiter, eds. Plenum, London , pp. 107–117.

[34] Kudupudi V, Kakarparthy RS, Sarella PN, Kolapalli VR. Formulation Development and Characterization of Vancomycin Hydrochloride Colon-Targeted Tablets Using In-Situ Polyelectrolyte Complexation Technique. International Journal of Pharmaceutical Sciences and Nanotechnology (IJPSN). 2023 May 31;16(3):6533-45.

[35] Sarella PN, Dadishetti JP, Asogwa PO, Kakarparthy R. A Case Report on Organic Psychosis Induced by Antitubercular Drugs in A Young Female. Asian Journal of Hospital Pharmacy. 2023 May 28:1-3.

[36] Maestroni, G.J.M., A. Conti, W. Pierpaoli (1986) Role of the pineal gland in immunity. Circadian synthesis and release of melatonin modulates the antibody response and antagonizes the immunosuppressive effect of corticosterone. J. Neuroimmunol. 13: 19–30.

[37] Reiter, R.J. (1974) Pineal regulation of hypothalamicopituitary axis: gonadotropins. In: Handbook of Physiology. E. Knobil, C. Sawyer, eds. American Physiological Society, Bethesda , Vol 4, pp. 519–550.

[38] Shavit, Y. (1991) Stress-induced immune modulation in animals: opiates and endogenous opioid peptides. In: Psychoneuroimmunology II. R. Ader, D.L. Felten, N. Cohen, eds. Academic Press, San Diego , pp. 789–807.

[39] Csaba, G., M. Bodoky, J. Fischer, T. Acs (1965) The effect of pineal ectomy and thymectomy on the immune capacity of the rat. Experientia 22: 168–175.

[40] Sarella PN, Vipparthi AK, Valluri S, Vegi S, Vendi VK. Nanorobotics: Pioneering Drug Delivery and Development in Pharmaceuticals. Research Journal of Pharmaceutical Dosage Forms and Technology. 2024 Feb 22;16(1):81-90.

[41] Maestroni, G.J.M., A. Conti, W. Pierpaoli (1987a) The pineal gland and the circadian opiatergic immunoregulatory role of melatonin. Ann. N.Y. Acad. Sci. 496: 67–77.

[42] Sibinga, N.E.S., A. Goldstein (1988) Opioid peptides and opioid receptors in cells of the immune system. Annu. Rev. Immunol. 6: 219–249.

[43] Csaba, G., P. Barath (1975) Morphological changes of thymus and the thyroid gland after postnatal extirpation of pineal body. Endocrinol. Exper. 9: 59–67.

[44] Deguchi, T., J. Axelrod (1973) Control of circadian change of serotonin N-acetyltransferase in the pineal organ by β-adrenergic receptor. Proc. Natl. Acad. Sci. U.S.A. 70: 2411–2414.

[45] Maestroni, G.J.M., A. Conti, W. Pierpaoli (1987b) Role of the pineal gland in immunity. II. Melatonin enhances the antibody response via an opiatergic mechanism. Clin. Exp. Immunol. 68: 384–391.

[46] Mangam VT, Nallam VR, Anitha A, Devi PR, Sanisha M. Dengue-An Overview. International Journal of Pharma Research. 2018 Jan 1;9(1).

[47] Maestroni, G.J.M., A. Conti (1991b) Role of the pineal neurohormone melatonin in the psycho-neuroendocrine immune network. In: Psychoneuroimmunology II. R. Ader, D.L. Felten, N. Cohen, eds. Academic Press, San Diego , pp. 495–513.

[48] Del Gobbo, V., V. Libri, N. Villani, R. Calio, G. Nistico (1989) Pinealectomy inhibits interleukin-2 production and natural killer activity in mice. Int. J. Immunopharacol. 11: 567–577.

[49] Maestroni, G.J.M., A. Conti, W. Pierpaoli (1988a) Pineal melatonin: Its fundamental immunoregulatory role in aging and cancer. Ann. N.Y. Acad. Sci. 521: 140 148.

[50] Waldenling, E., S.A. Gustafsson, K. Ekbom, L. Wetter-BERG (1987) Circadian secretion of cortisol and melatonin in cluster headache during active cluster periods and remission. J. Neurol. Neurosurg. Psychiatry 50: 207–214.

[51] Withyachumnarnkul, B., K.O. Nonaka, C. Santana, A.M. Attia, R.J. Reiter (1990). Interferon-gamma modulates melatonin production in rat pineal gland in organ culture. J. Interferon Res. 10: 403–411.

[52] Maestrons, G.J.M., A. Conti, W. Pierpaoli (1989) Melatonin, stress, and the immune system. In: Pineal Research Reviews, Vol. 7. R.J. Reiter, ed. Alan R. Liss, New York , pp. 203–223.

[53] Maestroni, G.J.M., A. Conti (1991a) Anti-stress role of the melatonin-immuno-opioid network. Evidence for a physiological mechanism involving T cell-derived, immunoreactive β-endorphin and met-enkephalin binding to thymic opioid receptors. Int. J. Neurosci. 61: 289–298.

[54] Maestroni, G.J.M., A. Conti (1993) Melatonin in relation with the immune system. In: Melatonin: Biosynthesis, Physiological Effects and Clinical Applications. Y. Hing-Su, R.J. Reiter, eds. CRC Press, Boca Raton , pp. 289–311.

Author's short biography

Imran Rashid

With a background in pharmacy research, Imran Rashid's scholarly pursuits seamlessly intertwine groundbreaking pharmacological advancements with ethical considerations, providing insights into the ever-evolving landscape of pharmaceutical innovation.

Mashooq Ah Mir

UG Scholar studying BPharmacy in RIMT university, exploring emerging trends and advancements in pharmaceutical sciences and research.

Aaliya Andleeb

UG Scholar studying BPharmacy in RIMT university, with a keen interest in pharmaceutical technology and the utilization of modern analytical tools

Abhishek Kumar

UG Scholar studying BPharmacy in RIMT university, channels his passion into exploring the intricacies of cellular and molecular pharmacology

Umehear Munshi

UG Scholar studying BPharmacy in RIMT university, harbors aspirations of becoming a clinical pharmacist, actively engaging in drug design and participating in clinical trials

Danish Habib

UG Scholar studying BPharmacy in RIMT university, delves into the latest methodologies and validation processes for newly FDA-approved drugs, contributing to the forefront of pharmaceutical research

Subzar Ahmad

UG Scholar studying BPharmacy in RIMT university, interests lie in the realm of pharmaceutical research, where he amalgamates scientific precision with contemporary advancements, shaping the future of pharmacology