International Journal of
Case Reports & Short Reviews

Case Report

Melatonin: The Continuing Neuroprotective Promise of a Versatile Molecule -

Leonor Chacin-Bonilla*, Ricardo Cardenas and Ernesto Bonilla

Instituto de Investigaciones Clinicas, Universidad del Zulia, Apartado Postal 23 Maracaibo 4001-A, Venezuela

***Address for Correspondence:** Leonor Chacin-Bonilla, Instituto de Investigaciones Clinicas, Universidad del Zulia, Apartado Postal 23 Maracaibo 4001-A, Venezuela, Tel: +58-202-340-1787; ORCID: orcid.org/0000-0002-8203-3185; E-mail: leonorbonilla42@yahoo.com

Submitted: 06 December 2022; **Approved:** 13 December 2022; **Published:** 14 December 2022

Cite this article: Chacin-Bonilla L, Cardenas R, Bonilla E. Melatonin: The Continuing Neuroprotective Promise of a Versatile Molecule. Int J Case Rep Short Rev, 2022 Dec 14; 8(1): 009-012. doi: 10.37871/ijcrsr.id99

ISSN: 2638-9355

ABSTRACT

Melatonin, a highly conserved indole neurohormone, is synthesized in different tissues and organs, exerting distinct functions, acting as an antioxidant and immunoregulatory agent, but also demonstrating neuroprotective and neurogenesis stimulating properties. Due to its pleiotropism, and its known safety profile, the indole has been evaluated as a potential therapeutic option in numerous pathological conditions. In this sense, a significant amount of effort has been put into studying the use of melatonin in the treatment of neurodegenerative diseases, including Alzheimer´s disease, Parkinson´s disease and Multiple Sclerosis, since, amongst other phenomena, these and related disorders are characterized by an increase in oxidative stress in the central nervous system, along with extensive and premature neuronal death. This short review aims to highlight recent findings which will help guide future research in determining the efficacy of melatonin as a solid clinical option for the treatment of neurodegenerative diseases.

Keywords: Melatonin; Pleiotropism; Parkinson´s disease; Alzheimer´s disease; Multiple sclerosis

INTRODUCTION

Melatonin (MEL) is a highly conserved, ubiquitous indole, observed from unicellular organisms to complex multicellular species in humans, it was first reported as synthesized by the pineal gland in the Central Nervous System (CNS), but it is produced in several tissues and organs, including the immune system and the gastrointestinal tract. Due to its chemical structure and functional properties, MEL can act upon specific receptors expressed in different tissues but also mediate its actions via receptor-independent means, including the direct interaction with substances such as free radicals and elements of the mitochondria. The presence of the molecule in distinct tissues, and its pleiotropic nature, has led numerous groups of research to study the participation and potential therapeutic implications of melatonergic pathways in diverse disorders, including psychiatric and Neurodegenerative Diseases (NDs), autoimmune disorders, chronic inflammatory syndromes, and oncology MEL, as an endogenous mediator with free radical-detoxifying properties within cells promoting sleep and regulation of circadian rhythms an important immune modulatory, antioxidant, anti-inflammatory and neuroprotective effects, has been also studied as an option for the treatment of different infectious agents [1].

In the last few years, promising findings on the antioxidant, immunoregulatory and neuroprotective features of MEL, along with its proven safety profile, have contributed to support the use of indole for the treatment of disorders such as Parkinson's Disease (PD), Alzheimer's Disease (AD) and Multiple Sclerosis (MS) however, more conclusive data is needed. The aim of this short review is to highlight the results of recent studies which will help guide future research to determine the reliability of MEL as an effective option for the treatment of certain NDs.

Effects of Melatonin on Oxidative Stress, Mitochondria and Aging

The antioxidant properties of MEL have been extensively studied, in a variety of conditions in which oxidative stress is a common trait, both at the local tissue and the systemic level; the results support the use of the indole in reducing the concentration of free radicals and the subsequent tissue damage. Thus, in a model of streptozotocin-induced diabetes in rats, additionally exposed to acute swimming exercise, intraperitoneal supplementation of MEL for 4 weeks prevented damage to bone tissue associated with oxidative stress, suppressing Malondialdehyde (MDA) production, and increasing Glutathione (GSH) levels [2]. Administration of the indole has likewise been evaluated in animal models of testicular torsion-detorsion in effect torsion causes ischemia while detorsion is followed by reperfusion leading to free radical production and tissue damage ipsilateral and contralateral. It was reported that prophylactic MEL, before testicular torsion in rats reduced ipsilateral and contralateral testicular MDA levels [3]; similarly 3 weeks of intraperitoneal zinc and MEL, in a testicular torsion-detorsion model in rats, demonstrated that either zinc alone, MEL alone, or their combination, helped reduce MDA levels, increase GSH levels, and maintain levels of inhibin-B and spermatogenic activity [4]. Finally, the effect of the neurohormone has been studied with regards to oxidative stress in a rat model of hyperthyroidism; in rats with hyperthyroidism, the concentration of brain, liver and heart MDA was substantially higher versus controls on the contrary, in animals with hyperthyroidism which received intraperitoneal treatment with MEL, MDA values were significantly lower and GSH levels were considerably higher when compared with pharmacological controls [5].

The participation and potential therapeutic applications of MEL in NDs have been studied in animal models and in humans, with special emphasis on the effect of the indole on oxidative stress; in this regard, a reduction in pineal and tissue MEL appears to be a biomarker of aging and could indicate the presence of neurodegenerative processes analogous to aging. In patients with Tardive Dyskinesia (TD), which is a consequence among other factors of oxidative stress caused by free radicals related to the use of antipsychotic treatment with MLT for 12 weeks was associated with clinical improvement was observed in some of the subjects [6]. In the context of PD, mitochondrial dysfunction and oxidative stress are extensively linked to the pathogenesis of the disease, particularly considering that the respiratory chain complex I is the fundamental site of mitochondrial superoxide production. Animal models of paraquat toxicity is used to better understand the occurrence and progression of PD; paraquat generates superoxide radicals in isolated mitochondria, and in *Caenorhabditis elegans*, rodents and *Drosophila melanogaster* the toxic effect of the substance is long lasting and in the case of flies, it affects motor activity. Administration of MEL to D. melanogaster exposed to paraquat has been reported to extend the life span of the animals, when compared to controls furthermore, MEL has an antioxidant effect on flies treated with paraquat, with reduced Super Oxide Dismutase (SOD) and catalase activity, and diminished H_2O_2 and mitochondrial MDA levels [7]. Likewise, in a model of cognitive decline in aged rats co-administration of Nicotinamide Mono Nucleotide (NMN) and MEL reduced apoptosis and mitochondrial dysfunction in the prefrontal cortex and the hippocampus, improving learning and memory deficits. The authors proposed that the combination could exert neuroprotection due to an antioxidant effect and the inhibition of mitochondrial permeability [8].

It has been reported that systemic MEL can elicit its effects in a receptor-independent or dependent manner similarly, the

DOI: https://dx.doi.org/10.37871/ijcrsr.id99

neuroprotective effects of MEL appear to be similar, whether receptor mediated or independently, with both pathways capable of promoting antioxidant mechanisms, scavenge free radicals, and protect the mitochondria [9]. Treatment with melatonin for three months demonstrated to reduce plasma nitric oxide metabolites, lipoperoxides and carbonyl groups while catalase activity was augmented, when compared with placebo, in a double-blind, cross-over, placebo-controlled randomized clinical trial in 26 patients with PD likewise, treatment with MEL was associated with an increase in the activity of the mitochondrial complex 1 [10]. Intriguingly, a study with cell cultures indicated that there exists a relationship between certain parts of the molecule and particular properties thus, the tryptamine core would seem fundamental for the neuroprotective role of the indole and even if removal of the N-acetyl group improves neuroprotection, it could affect the safety profile of the molecule. [11]. A tailored approach to designing indole-derived candidate drugs could be based on these and similar findings.

Effect on Inflammatory Markers and Neuroprotection

Studying the effect of MEL on viral infections has greatly contributed to better illustrate the connection between the diverse features of the molecule; thus, in a model of Venezuelan Equine Encephalitis (VEE) virus infection in mice MEL has been proven to diminish death rate limit the evolution of the disease the neurohormone also stimulates the immune response, with an increase in IgM titers in blood in animals vaccinated against the virus with multiple doses of the indole coinciding with a substantial increase in the concentration of IL-10 [12,13]. In a related study, in the same model of VEE infection, it was proposed that the protective effect of MLT could be explained by an immunoregulatory effect in the context of the infection, with decreased levels of TNF-α and increased levels of IL-1β; said modulation would be aimed at reducing the inflammatory response in the CNS, along with recovering the normal function of the blood brain barrier [14]. In this regard studies in other animal models linking the occurrence of viral infections with neurodegeneration, have shown that MLT could have a neuroprotective effect this is of significant relevance, since neurodegeneration has been associated with several infections, and MLT could then help prevent neuronal loss in these instances. Porcine induced Neural Stem Cells (iNSCs) were used for evaluation of the protective effect of MLT against chemical and pathogenic degeneration. The cells were treated with MLT prior to induced degeneration with Dimethyl Sulfoxide (DMSO) or Zika Virus (ZIKV); the results showed that MLT protected porcine iNSCs from DMSO-induced degeneration as well as reducing the percentage of dead porcine iNSCs after ZIKV infection, although replication of the virus itself within the cells was not modified by MLT [15].

Potential Clinical Applications of Melatonin in Neurodegeneration

In early phases of PD, the aberrant phosphorylation and accumulation of α-synuclein is a key process, leading to cellular oxidative stress and mitochondrial dysfunction. Novel drug delivery systems, such as MLT enriched polydopamine nanostructures, have been shown to secure superior brain targeting, neuroprotection, antioxidant and anti-inflammatory effects, and reduced deposition of α-synuclein in the hippocampus and substantia nigra, with increased MLT release, preventing dopaminergic cell death in *in vitro* models [16]. Several studies have shown alterations in MLT levels, with decrease in AD patients compared with age-matched controls, reduced levels when compared with preclinical values in cerebrospinal fluid samples, flattened diurnal MLT curve, and sleep disturbances. In animal models, MEL has been shown to exert neuroprotection, counteracting oxidative stress, lipid peroxidation, and abnormal mitochondrial function, which could reduce AD neuropathology and eventually delay or prevent AD progression, and in transgenic rodent models of AD, MEL has led to improved learning and memory. In humans, findings vary between groups: retrospective studies have shown the beneficial effects of MLT administered for several months, in cognition and sleep, in mild cognitive impairment, and double-blind, placebo-controlled studies have indicated that MEL can diminish agitated behavior, reduce sleep onset, and elevate sleep duration in patients with AD; however, other randomized controlled trials have shown no effect. Certain factors could affect the response to MLT, including differing administration regimens, variation in the bioavailability of OTC presentations of MLT, as well as safety concerns. Of equal importance, from a methodological point of view, future studies must establish whether MLT affects the pharmacodynamics and pharmacokinetics of other CNS-acting drugs, particularly considering the likelihood that patients with AD or other ND must often take several drugs simultaneously; with these factors into account, the design of large randomized, placebo-controlled studies, will help clarify the usefulness of MLT as part of treatment regimens [17].

In AD, PD and other NDs, MEL has been shown to increase cell survival in specific brain regions; as a scavenger of free radicals, the indole modulates the neuroinflammatory response, diminishes oxidative stress, and might even directly interact with β-amyloid, preventing its aggregation; learning and memory impairment in a mouse model of AD can be improved by MEL. Prophylactically, MEL can induce expression of neurotrophic factors and stimulate cholinergic transmission in the brain cortex; concomitantly, the neurohormone is able to reduce age-related cognitive impairment; chronic administration has been shown to reduce the concentration of proinflammatory cytokines in old mice; and in models of chronic stress, it has been demonstrated to enhance neurogenesis and synaptogenesis, along with inducing antioxidant and antiapoptotic mechanisms within neurons. However, it is essential to further explore the precise mechanisms underlying the action of the indole in NDs, and, more importantly, whether combining MEL with other agents could potentiate its effects [18]. In MS, administration of MEL increases neurogenesis and transcriptional markers that lead to neuron survival in the mouse hippocampus; disrupted MLT secretion may play a role in MS pathogenesis, and certain gene variants have been associated with abnormal MLT secretion. Nevertheless, given the association between MS and comorbidities such as anxiety, depression, and sleep disturbances, and despite the encouraging results which indicate beneficial antioxidant and immunoregulatory effects in MS, only a small number of clinical trials have tested the efficacy of MLT supplementation in MS treatment; there exist ample opportunities for research in this area [19].

Future Research

Animal and *in vitro* findings have highlighted the physiopathological relevance of the indole, and in the future, results from different types of studies will continue helping elucidate the relevant mechanisms underlying the clinically impactful procognitive and neuroprotective properties of MEL. Upcoming research efforts must focus on establishing the most effective way of implementing the features of the neurohormone in everyday clinical practice with well-designed, methodologically and statistically reliable clinical trials, to

DOI: https://dx.doi.org/10.37871/ijcrsr.id99

help decide how best to incorporate MEL, with its affordability and its safety profile, into useful therapeutic regimens.

CONCLUSION

In the context of the CNS, the pleiotropism of MEL extend to its neuroprotective and neurogenesis-stimulating properties. Since extensive and premature neuronal death is a key feature in most NDs, especially in AD, PD and MS and considering the antioxidant, immunoregulatory and neuroprotective properties of the indole, the prospect of effectively applying these features would represent a significant improvement in the lives of patients afflicted with NDs.

ACKNOWLEDGMENT

Authorship

All authors contributed to the conceptualization, writing, and editing of this manuscript.

Funding

No funding was received for this study.

Conflicts of interest

The authors declare no conflict of interest.

REFERENCES

1. Vielma JR, Bonilla E, Chacín-Bonilla L, Mora M, Medina-Leendertz S, Bravo Y. Effects of melatonin on oxidative stress, and resistance to bacterial, parasitic, and viral infections: a review. Acta Trop. 2014 Sep;137:31-8. doi: 10.1016/j.actatropica.2014.04.021. Epub 2014 May 6. PMID: 24811367.
2. Bicer M, Baltaci SB, Patlar S, Mogulkoc R, Baltaci AK. Melatonin has a protective effect against lipid peroxidation in the bone tissue of diabetic rats subjected to acute swimming exercise. Horm Mol Biol Clin Investig. 2018 Mar 16;34(2):/j/hmbci.2018.34.issue-2/hmbci-2017-0079/hmbci-2017-0079.xml. doi: 10.1515/hmbci-2017-0079. PMID: 29547389.
3. Ozturk A, Baltaci AK, Mogulkoc R, Ozturk B. The effect of prophylactic melatonin administration on reperfusion damage in experimental testis ischemia-reperfusion. Neuro Endocrinol Lett. 2003 Jun-Aug;24(3-4):170-2. PMID: 14523352.
4. Semercioz A, Baltaci AK, Mogulkoc R, Avunduk MC. Effect of Zinc and Melatonin on Oxidative Stress and Serum Inhibin-B Levels in a Rat Testicular Torsion-Detorsion Model. Biochem Genet. 2017 Dec;55(5-6):395-409. doi: 10.1007/s10528-017-9826-5. Epub 2017 Nov 1. PMID: 29094225.
5. Mogulkoc R, Baltaci AK, Oztekin E, Aydin L, Sivrikaya A. Melatonin prevents oxidant damage in various tissues of rats with hyperthyroidism. Life Sci. 2006 Jun 13;79(3):311-5. doi: 10.1016/j.lfs.2006.01.009. Epub 2006 Feb 7. PMID: 16464477.
6. Castro F, Carrizo E, Prieto de Rincón D, Rincón CA, Asián T, Medina-Leendertz S, Bonilla E. Effectiveness of melatonin in tardive dyskinesia. Invest Clin. 2011 Sep;52(3):252-60. PMID: 21950196.
7. Medina-Leendertz S, Paz M, Mora M, Bonilla E, Bravo Y, Arcaya JL, Terán R, Villalobos V. Longterm melatonin administration alleviates paraquat mediated oxidative stress in Drosophila melanogaster. Invest Clin. 2014 Dec;55(4):352-64. PMID: 25558754.
8. Hosseini L, Farokhi-Sisakht F, Badalzadeh R, Khabbaz A, Mahmoudi J, Sadigh-Eteghad S. Nicotinamide Mononucleotide and Melatonin Alleviate Aging-induced Cognitive Impairment via Modulation of Mitochondrial Function and Apoptosis in the Prefrontal Cortex and Hippocampus. Neuroscience. 2019 Dec 15;423:29-37. doi: 10.1016/j.neuroscience.2019.09.037. Epub 2019 Oct 31. PMID: 31678348.
9. Melhuish Beaupre LM, Brown GM, Gonçalves VF, Kennedy JL. Melatonin's neuroprotective role in mitochondria and its potential as a biomarker in aging, cognition and psychiatric disorders. Transl Psychiatry. 2021 Jun 2;11(1):339. doi: 10.1038/s41398-021-01464-x. PMID: 34078880; PMCID: PMC8172874.
10. Jiménez-Delgado A, Ortiz GG, Delgado-Lara DL, González-Usigli HA, González-Ortiz LJ, Cid-Hernández M, Cruz-Serrano JA, Pacheco-Moisés FP. Effect of Melatonin Administration on Mitochondrial Activity and Oxidative Stress Markers in Patients with Parkinson's Disease. Oxid Med Cell Longev. 2021 Oct 18;2021:5577541. doi: 10.1155/2021/5577541. PMID: 34707777; PMCID: PMC8545577.
11. Letra-Vilela R, Sánchez-Sánchez AM, Rocha AM, Martin V, Branco-Santos J, Puente-Moncada N, Santa-Marta M, Outeiro TF, Antolín I, Rodriguez C, Herrera F. Distinct roles of N-acetyl and 5-methoxy groups in the antiproliferative and neuroprotective effects of melatonin. Mol Cell Endocrinol. 2016 Oct 15;434:238-49. doi: 10.1016/j.mce.2016.07.012. Epub 2016 Jul 9. PMID: 27402602.
12. Bonilla E, Valero-Fuenmayor N, Pons H, Chacín-Bonilla L. Melatonin protects mice infected with Venezuelan equine encephalomyelitis virus. Cell Mol Life Sci. 1997 May;53(5):430-4. doi: 10.1007/s000180050051. PMID: 9176561.
13. Negrette B, Bonilla E, Valero N, Pons H, Garcia Tamayo J, Chacín-Bonilla L, Medina-Leendertz S, Añez F. Melatonin treatment enhances the efficiency of mice immunization with Venezuelan equine encephalomyelitis virus TC-83. Neurochem Res. 2001 Jul;26(7):767-70. doi: 10.1023/a:1011645400123. PMID: 11565607.
14. Bonilla E, Valero N, Chacín-Bonilla L, Pons H, Larreal Y, Medina-Leendertz S, Espina LM. Melatonin increases interleukin-1beta and decreases tumor necrosis factor alpha in the brain of mice infected with the Venezuelan equine encephalomyelitis virus. Neurochem Res. 2003 May;28(5):681-6. doi: 10.1023/a:1022897314108. PMID: 12716016.
15. Horcharoensuk P, Yang-En S, Chakritbudsabong W, Samatiwat P, Pramong R, Rungarunlert S, Rungsiwiwut R. Melatonin attenuates dimethyl sulfoxide- and Zika virus-induced degeneration of porcine induced neural stem cells. In Vitro Cell Dev Biol Anim. 2022 Mar;58(3):232-242. doi: 10.1007/s11626-022-00648-z. Epub 2022 Mar 2. PMID: 35235152; PMCID: PMC8890020.
16. Srivastava AK , Roy Choudhury S , Karmakar S . Melatonin/polydopamine nanostructures for collective neuroprotection-based Parkinson's disease therapy. Biomater Sci. 2020 Mar 7;8(5):1345-1363. doi: 10.1039/c9bm01602c. Epub 2020 Jan 8. PMID: 31912833.
17. Alagiakrishnan K. Melatonin based therapies for delirium and dementia. Discov Med. 2016 May;21(117):363-71. PMID: 27355332.
18. Miranda-Riestra A, Estrada-Reyes R, Torres-Sanchez ED, Carreño-García S, Ortiz GG, Benítez-King G. Melatonin: A neurotrophic factor? Molecules. 2022;27:7742. doi: 10.3390/molecules27227742.
19. Skarlis C, Anagnostouli M. The role of melatonin in Multiple Sclerosis. Neurol Sci. 2020 Apr;41(4):769-781. doi: 10.1007/s10072-019-04137-2. Epub 2019 Dec 16. PMID: 31845043.

DOI: https://dx.doi.org/10.37871/ijcrsr.id99