Effects of Melatonin on Diabetic Neuropathy and Retinopathy

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Contributor: Klausen Oliveira Abreu

Diabetes mellitus (DM) leads to complications, including neuropathy. Redox imbalance and inflammation are important components of the pathophysiology of these complications. Many studies have investigated the therapeutic potential of melatonin (MEL), an anti-inflammatory and antioxidant agent, for the specific treatment of the neural complications. In the present entry, we review studies published over the past 21 years on the therapeutic efficacy of MEL in the treatment of DM-induced neural complications. Reports suggest that there is a real prospect of using MEL as an adjuvant treatment for hypoglycemic agents.

melatonin | diabetes mellitus | diabetic neuropathy | diabetic retinopathy

1. Introduction

Diabetes mellitus (DM) is a metabolic disorder characterized by hyperglycemia due to chronic or relative insulin deficiency. The main complications of DM are nephropathy, retinopathy, and neuropathy [1][2].

Diabetic neuropathy (DN) affects more than 50% of patients with diabetes and is a diabetic complication that affect the nervous system [3] whilst diabetic retinopathy (DR) affects the retina [4]. The few treatments available for DN and DR, are ineffective and have serious side effects. The compound melatonin (MEL) has been studied for the treatment of DM and its complications, such as DN and DR [4].

MEL is a hormone produced by the pineal gland. It has several pharmacological effects, such as: neuroprotective, anti-inflammatory, and inhibitory actions on the excitability of neurons in the central nervous system (CNS) and peripheral nervous system (PNS) [5][6][7]. Additionally, MEL has some effects opposite to those caused by DM. For example, MEL caused resting membrane potential (RMP) hyperpolarization, increased input resistance (R_{in}), and reduced excitability in dorsal root ganglia neurons [7][8]. DM, on the other hand, caused opposite effects [9].

2. Relationship of Melatonin with Diabetic Neuropathy and Retinopathy

2.1. Effect of Melatonin Treatment on Diabetic Neuropathy

DM causes an increase in oxidative stress, as informed by measurements of several markers, such as increased malondialdehyde (MDA), lipid peroxidation, and reduced levels of glutathione (GSH), superoxide dismutase (SOD),

and catalase. MEL has been shown to reverse the change in the levels of all of these markers, in addition to increasing the total antioxidant capacity (TAC) [10][11][12][13][14].

DM has been shown to increase the levels of inflammatory markers: Tumor Necrosis Factor alpha (TNF-α), interleukin 6 (IL-6), inducible nitric oxide synthase (iNOS), while treatment with MEL reverted these parameters to normal [13][15].

Baydas et al.[10] investigated the effect of MEL on glial reactivity. DM caused an increase in astrocyte function markers, observed in glial reactivity, while MEL reduced these levels.

Regarding clinical studies, Shokri et al. [16] investigated the efficacy of MEL as an adjuvant to pregabalin for pain relief in diabetic neuropathy. This study reported a considerable reduction in pain and pain-related sleep interference scores in MEL-treated patients. MEL acted through different mechanisms.

2.2. Effect of Melatonin Treatment on Diabetic Retinopathy

Regarding the effects of MEL on parameters related to oxidative stress (levels of nitrotyrosine, MDA, lipid peroxidation, and GSH) and inflammation (release of pro-inflammatory cytokines, such as TNF-α, IL-1β, iNOS, and IL-6) which were altered on animal models of DR, they were reversed by MEL [17][18][19][20][21]. Increase in the expression of MT_1 and MT_2 receptors in the retinas of diabetic rats was aldo documented [17].

A neuroprotective anti-apoptotic effect of MEL on the retinal neurons of diabetic rats was reported [22].

In experimental model of prediabetes, serum concentrations of MEL levels were found reduced and of pro-angiogenic molecules (vascular endothelial growth factor (VEGF) and matrix metalloproteinase 9 (MMP9)), increased. This was reversed with MEL supplementation [23] .

Thus, studies that evaluated the effect of MEL on experimental models of DR suggest that this hormone may exert a protective effect on the retina of diabetic animals through mechanisms similar to those reported in animals with DN, such as antioxidant and anti- inflammatory effects.

3. Conclusions

Based on the studies presented, there are clear indications that MEL has a beneficial effect on DN and DR and is therefore promising from a therapeutic point of view. However, there is a certain difficulty in developing a unified view, as the studies present different approaches of dosage, neural structure, and moment of DM time-course in a progressive degenerative disease.

Finally, according to the studies available MEL may be suggested as a promising molecule in the treatment of complications from diabetes mellitus, specifically, DN and DR.

References

1. American Diabetes Association; Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care* **2012**, *36*, S67-S74, 10.2337/dc13-s067.
2. Ann Marie Schmidt; Highlighting Diabetes Mellitus. *Arteriosclerosis, Thrombosis, and Vascular Biology* **2017**, *38*, e1-e8, 10.1161/atvbaha.117.310221.
3. Eva L. Feldman; Brian C. Callaghan; Rodica Pop-Busui; Douglas W. Zochodne; Douglas E. Wright; David L. Bennett; Vera Bril; James W. Russell; Vijay Viswanathan; Diabetic neuropathy. *Nature Reviews Disease Primers* **2019**, *5*, 41, 10.1038/s41572-019-0092-1.
4. Mohammad Hossein Pourhanifeh; Azam Hosseinzadeh; Ehsan Dehdashtian; Karim Hemati; Saeed Mehrzadi; Melatonin: new insights on its therapeutic properties in diabetic complications. *Diabetology & Metabolic Syndrome* **2020**, *12*, 1-20, 10.1186/s13098-020-00537-z.
5. Dun-Xian Tan; Russel Reiter; Lucien Manchester; Mei-Ting Yan; Mamdouh El-Sawi; Rosa Sainz; Juan Mayo; Ron Kohen; Mario Allegra; Rudiger Hardelan; et al. Chemical and Physical Properties and Potential Mechanisms: Melatonin as a Broad Spectrum Antioxidant and Free Radical Scavenger. *Current Topics in Medicinal Chemistry* **2002**, *2*, 181-197, 10.2174/1568026023394443.
6. Ahmet Korkmaz; Russel J. Reiter; Turgut Topal; Lucien C. Manchester; Sukru Oter; Dun-Xian Tan; Melatonin: An Established Antioxidant Worthy of Use in Clinical Trials. *Molecular Medicine* **2008**, *15*, 43-50, 10.2119/molmed.2008.00117.
7. Klausen Oliveira-Abreu; Francisco Walber Ferreira-Da-Silva; Kerly Shamyra Da Silva-Alves; Nathalia Maria Silva-Dos-Santos; Ana Carolina Cardoso-Teixeira; Fernanda Gaspar Do Amaral; Jose Cipolla-Neto; José Henrique Leal-Cardoso; Melatonin decreases neuronal excitability in a sub-population of dorsal root ganglion neurons. *Brain Research* **2018**, *1692*, 1-8, 10.1016/j.brainres.2018.04.027.
8. Klausen Oliveira-Abreu; Nathalia Maria Silva-Dos-Santos; Andrelina Noronha Coelho-De-Souza; Francisco Walber Ferreira-Da-Silva; Kerly Shamyra Da Silva-Alves; Ana Carolina Cardoso-Teixeira; José Cipolla-Neto; José Henrique Leal-Cardoso; Kerly Silva-Alves; Melatonin Reduces Excitability in Dorsal Root Ganglia Neurons with Inflection on the Repolarization Phase of the Action Potential.. *International Journal of Molecular Sciences* **2019**, *20*, 2611, 10.3390/ijms20112611.
9. Nathalia Maria Silva-Dos-Santos; Klausen Oliveira-Abreu; Luiz Moreira-Junior; Tiago dos Santos-Nascimento; Kerly Shamyra da Silva-Alves; Andrelina Noronha Coelho-De-Souza; Francisco Walber Ferreira-Da-Silva; José Henrique Leal-Cardoso; Diabetes mellitus alters electrophysiological properties in neurons of superior cervical ganglion of rats. *Brain Research* **2020**, *1729*, 146599, 10.1016/j.brainres.2019.146599.

10. Giyasettin Baydas; Russel J Reiter; Abdullah Yasar; Mehmet Tuzcu; Ismail Akdemir; Viktor S Nedzvetskii; Melatonin reduces glial reactivity in the hippocampus, cortex, and cerebellum of streptozotocin-induced diabetic rats. *Free Radical Biology and Medicine* **2003**, *35*, 797-804, 10.1016/s0891-5849(03)00408-8.
11. Begum Gurel-Gokmen; Hazal Ipekci; Sehkar Oktay; Burcın Alev; Unsal Velı Ustundag; Esın Ak; Dılek Akakın; Goksel Sener; Ebru Emekli-Alturfan; Aysen Yarat; et al.Tugba Tunali-Akbay Melatonin improves hyperglycemia induced damages in rat brain. *Diabetes/Metabolism Research and Reviews* **2018**, *34*, e3060, 10.1002/dmrr.3060.
12. Ashok Jangra; Ashok Kumar Datusalia; Shriya Khandwe; Shyam Sunder Sharma; Amelioration of diabetes-induced neurobehavioral and neurochemical changes by melatonin and nicotinamide: Implication of oxidative stress–PARP pathway. *Pharmacology Biochemistry and Behavior* **2013**, *114-115*, 43-51, 10.1016/j.pbb.2013.10.021.
13. Adham M. Maher; Samar R. Saleh; Nihal Elguindy; Hagar M. Hashem; Galila A. Yacout; Exogenous melatonin restrains neuroinflammation in high fat diet induced diabetic rats through attenuating indoleamine 2,3-dioxygenase 1 expression. *Life Sciences* **2020**, *247*, 117427, 10.1016/j.lfs.2020.117427.
14. Mohamed M.M. Metwally; Lamiaa L.M. Ebraheim; Azza A.A. Galal; Potential therapeutic role of melatonin on STZ-induced diabetic central neuropathy: A biochemical, histopathological, immunohistochemical and ultrastructural study. *Acta Histochemica* **2018**, *120*, 828-836, 10.1016/j.acthis.2018.09.008.
15. Geeta Negi; Ashutosh Kumar; Shyam S. Sharma; Melatonin modulates neuroinflammation and oxidative stress in experimental diabetic neuropathy: effects on NF-κB and Nrf2 cascades. *Journal of Pineal Research* **2010**, *50*, 124-131, 10.1111/j.1600-079x.2010.00821.x.
16. Maryam Shokri; Firozeh Sajedi; Younes Mohammadi; Maryam Mehrpooya; Adjuvant use of melatonin for relieving symptoms of painful diabetic neuropathy: results of a randomized, double-blinded, controlled trial. *European Journal of Clinical Pharmacology* **2021**, *77*, 1649-1663, 10.1007/s00228-021-03170-5.
17. Tingting Jiang; Qing Chang; Jiyang Cai; Jiawen Fan; XiaoZhe Zhang; Gezhi Xu; Protective Effects of Melatonin on Retinal Inflammation and Oxidative Stress in Experimental Diabetic Retinopathy. *Oxidative Medicine and Cellular Longevity* **2016**, *2016*, 1-13, 10.1155/2016/3528274.
18. Saeed Mehrzadi; Manijeh Motevalian; Mozhgan Rezaei Kanavi; Iman Fatemi; Habib Ghaznavi; Mansoor Shahriari; Protective effect of melatonin in the diabetic rat retina. *Fundamental & Clinical Pharmacology* **2018**, *32*, 414-421, 10.1111/fcp.12361.
19. G Özdemir; Y Ergün; S Bakariş; M Kılınç; H Durdu; E Ganiyusufoğlu; Melatonin prevents retinal oxidative stress and vascular changes in diabetic rats. *Eye* **2014**, *28*, 1020-1027, 10.1038/eye.20

14.127.

20. Ismaela Maria Ferreira de Melo; Cintia Giselle Martins Ferreira; Elton Hugo Lima Da Silva Souza; Lecio Leone Almeida; Fabrício Bezerra de Sá; Clovis José Cavalcanti Lapa Neto; Matheus Vinicius Paz de Castro; Valéria Wanderley Teixeira; Álvaro Aguiar Coelho Teixeira; Melatonin regulates the expression of inflammatory cytokines, VEGF and apoptosis in diabetic retinopathy in rats. *Chemico-Biological Interactions* **2020**, *327*, 109183, 10.1016/j.cbi.2020.109183.
21. Yuanyuan Tu; Manhui Zhu; Zhenzhen Wang; Kun Wang; Lili Chen; Wangrui Liu; Qin Shi; Qingliang Zhao; Yake Sun; Xiaoyu Wang; et al.E. SongXiaojuan Liu Melatonin inhibits Müller cell activation and pro-inflammatory cytokine production via upregulating the MEG3/miR-204/Sirt1 axis in experimental diabetic retinopathy. *Journal of Cellular Physiology* **2020**, *235*, 8724-8735, 10.1002/jcp.29716.
22. Xiaoyan Li; Maonian Zhang; Weiqiang Tang; Effects of Melatonin on Streptozotocin-Induced Retina Neuronal Apoptosis in High Blood Glucose Rat. *Neurochemical Research* **2013**, *38*, 669-676, 10.1007/s11064-012-0966-z.
23. Branka Djordjevic; Tatjana Cvetkovic; Tatjana Jevtovic Stoimenov; Milena Despotovic; Slavoljub Zivanovic; Jelena Basic; Andrej Veljkovic; Aleksandra Velickov; Gordana Kocic; Dusica Pavlovic; et al.Dusan Sokolovic Oral supplementation with melatonin reduces oxidative damage and concentrations of inducible nitric oxide synthase, VEGF and matrix metalloproteinase 9 in the retina of rats with streptozotocin/nicotinamide induced pre-diabetes. *European Journal of Pharmacology* **2018**, *833*, 290-297, 10.1016/j.ejphar.2018.06.011.
24. Xiaoyan Li; Maonian Zhang; Weiqiang Tang; Effects of Melatonin on Streptozotocin-Induced Retina Neuronal Apoptosis in High Blood Glucose Rat. *Neurochemical Research* **2013**, *38*, 669-676, 10.1007/s11064-012-0966-z.
25. Branka Djordjevic; Tatjana Cvetkovic; Tatjana Jevtovic Stoimenov; Milena Despotovic; Slavoljub Zivanovic; Jelena Basic; Andrej Veljkovic; Aleksandra Velickov; Gordana Kocic; Dusica Pavlovic; et al.Dusan Sokolovic Oral supplementation with melatonin reduces oxidative damage and concentrations of inducible nitric oxide synthase, VEGF and matrix metalloproteinase 9 in the retina of rats with streptozotocin/nicotinamide induced pre-diabetes. *European Journal of Pharmacology* **2018**, *833*, 290-297, 10.1016/j.ejphar.2018.06.011.