REVIEW ARTICLE

Melatonin and organ transplantation: what is the relationship?

Carolina F. Haddad[1]
Jorge M. Haddad[1]
Eduardo Carvalho de Arruda Veiga[1]
Isabel Cristina Esposito Sorpreso[1]
Ricardo Santos Simões[1]
Edmund Chada Baracat[1]
José Maria Soares-Júnior[1]

1. Disciplina de Ginecologia, Departamento de Obstetrícia e Ginecologia, Hospital das Clínicas, Faculdade de Medicina da Universidade de São Paulo.

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SUMMARY

Melatonin has anti-inflammatory and antioxidant properties that can influence tissue growth and apoptosis. This aspect may influence the success of organ transplantation.

OBJECTIVE: *To evaluate the relationship between melatonin and organ transplantation.*

METHODS: *A systematic review was performed in PubMed databases using the search terms: "melatonin physiology" or "melatonin therapy" and "transplant pharmacology" or "transplant physiology" or "transplant therapy" or "Transplant therapy". Experiments on the organs of the reproductive system were not included. After analysis, five articles were selected after reading the title and abstract of 50 manuscripts. The works were divided into two aspects: a) analysis of the influence of the organ transplantation procedure on melatonin production; b) action of melatonin on organ transplantation.*

RESULTS: *The cardiac transplantation surgical procedure, immunosuppression, and graft did not influence melatonin secretion in rodents, but there was a significant reduction of melatonin in the renal transplantation procedure in patients with renal insufficiency. Melatonin administration in experimental models decreased rejection and improved transplant success.*

CONCLUSION: *Studies show that melatonin can reduce organ and species dependence, and the use of melatonin decreases graft rejection.*

KEYWORDS: *Melatonin. Oxidative stress. Transplants.*

INTRODUCTION

Melatonin is an indolamine produced mainly by pineal gland[1,2], which has a potent activity to neutralize free radicals due to its antioxidant and antiapoptotic functions[1,3,4]. Due to its hydrophilic and lipophilic affinity, melatonin can diffuse widely in various cellular compartments such as membranes, cytoplasm, nucleus, and mitochondria[1,4]. Thus, it can perform its antioxidant action quickly and effectively, soon after the production of these agents, which are harmful to the viability of tissues[5].

Some studies point out that one of the main challenges to achieving a successful transplant with less graft loss is the reduction of free radicals produced by the procedure[6], especially caused by

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CORRESPONDING AUTHOR: Eduardo Carvalho de Arruda Veiga
Departamento de Obstetrícia e Ginecologia, Hospital das Clínicas, Faculdade de Medicina da Universidade de São Paulo, FMUSP
Av. Dr. Enéas de Carvalho Aguiar, 255 - Prédio do Instituto Central, 10 andar, sala 10167 - São Paulo, SP, Brasil - 05403-000
E-mail: eduveiga56@gmail.com

ischemia-reperfusion stress[5]. Therefore, melatonin may block fatty acid uptake and would have multiple antioxidant actions, such as the removal of pro-oxidative enzymes, prevention of calcium overload and mitochondrial damage, and inhibition of cyclooxygenase[4-6]. Thus, it may reject grafts, promoting cellular repair, and removing reactive oxygen species[7]. Also, melatonin has immunological and antiapoptotic properties that are necessary for successful organ transplantation[5]. In the reproductive system, Shiroma et al.[8] showed that melatonin increases the success of ovarian transplantation. Therefore, this systematic review aims to evaluate the connection between melatonin and non-reproductive organ transplantation (uterus and ovary).

METHODS

The systematic review of studies that show the relationship between melatonin and organ transplantation, excluding those of the reproductive system (uterus and ovary) was conducted according to the recommendations established by PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis)[9]. For the identification of relevant studies, Medline primary database queries were conducted from January 1992 to May 2019, without restriction on the year of publication.

PICO was elaborated as follows: P (patient or experimental model): patients or animals that underwent organ transplantation, I (intervention): a) impact of the transplantation procedure on melatonin production; b) administration of melatonin on transplantation success; C (comparison): control group, and O (outcome): the relationship between melatonin and organ transplantation. The retrieval of articles was conducted through the search strategies described in Figure 1. The bibliographic references of the articles surveyed were also searched (data retrieval).

The selection of studies, the evaluation of titles and abstracts obtained from the search strategies in the consulted databases were conducted by two researchers (C.F.H. and R.S.S.) independently and blindly, strictly following the inclusion and exclusion criteria. After this step, the original article was critically evaluated to decide whether to include it or not in the review. When there was disagreement about study selection among investigators, a third reviewer was consulted (J.M.S.J).

The following inclusion criteria were used to identify relevant sources: (a) full text available; (b) articles in Portuguese, English, Spanish, or French; and (c) studies that used objective instruments to evaluate the relationship between melatonin and organ transplantation. Reproductive system manuscripts such as "ovary" and "uterus" were excluded, as well as duplicate manuscripts or narrative or systematic reviews.

The information obtained from the articles that make up the systematic review were shown in Tables 1 and 2, grouping: authors' name and year of publication, species, groups, objective, method, and outcome.

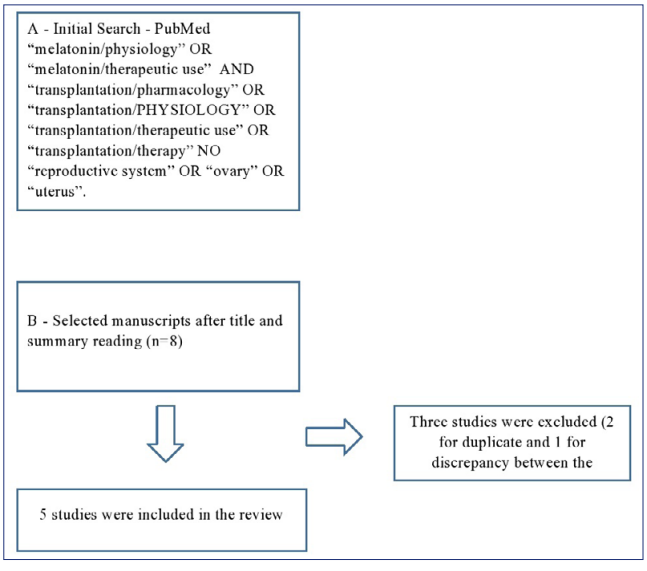
The analysis followed the PRISMA statement for systematic reviews[15]. Eight studies were identified by this research. After a detailed analysis of the manuscript contents, three were excluded: a) duplicate (n = 2); b) discrepancy about the analyzed subject (n = 1) (Fig. 1). Meta-analysis could not be performed due to the small number of studies.

RESULTS

Data on 126 rats and 210 patients were analyzed. In the studies, three rats were reported killed in one experimental study. In the remainder, there were no other complications or mortality. Two studies[10,11] aimed to evaluate the effects of organ transplantation procedure on melatonin production, while the other three[12-14] analyzed the effects of melatonin administration on heart or lung transplantation.

Regarding the first evaluation (impact of the transplantation procedure on melatonin production), as can

FIGURE 1. A) SEARCH STRATEGY AND B) SYSTEMATIC REVIEW ALGORITHM



be seen in Table 1, both manuscripts analyzed the relationship between organ transplantation and serum melatonin concentration. Viljoen et al.[10] showed a decrease in serum melatonin concentration after renal transplantation in patients with chronic renal failure. Cardell et al.[11] did not show significant changes in serum melatonin concentration after cardiac transplantation in rats.

The effects of melatonin on transplanted organs are summarized in Table 2. The beneficial effect of melatonin on short-term graft transplantation success (acute effect) is due to decreased oxidative stress, inflammatory process, and decreased apoptosis. The result is lower graft rejection in experimental studies.

Inci et al.[12] used a 10mg/kg dose of melatonin and observed a decrease in tissue damage after lung transplantation: a) smaller area of ischemia; b) reduced lipid peroxidation rate compared to the control; c) drop in lipid infiltration; d) reduction of tissue levels of glutathione oxidase and myeloperoxidase (MPO) activity; e) increased glutathione. Thus, some elements that suggest increased protection of the transplanted lung from the deleterious effects of reperfusion after ischemia.

Jung et al.[13] reported longer survival with reduced cellular and humoral immune response in rats treated with melatonin. This effect was dose-dependent. The lowest concentration of indolamine used was 20 mg/kg and the highest 200 mg/kg. There was a marked decrease in IgM concentration, proliferation, and graft rejection at the highest dose compared to the lowest dose and vehicle.

Santana-Rodríguez et al.[14] showed that melatonin (10 mg/kg) would improve radiological signs of severe respiratory failure in rats and longer graft survival. In this study, a group of animals was treated with estradiol (25mg / kg) and had the worst results: a) severe respiratory failure; b) increased inflammatory process; c) greater rejection; d) shorter survival with a high mortality rate of around 60%.

DISCUSSION

Melatonin has properties that reduce graft rejection, such as its anti-inflammatory and antioxidant effect[1-7]. This action had already been described for ovarian grafts[7]. Our studies have proven these actions in heart and lung transplantation in experimental models. Therefore, melatonin could be beneficial in reducing graft rejection. Regarding the influence of the transplantation procedure on melatonin production, it was shown that the serum reduction of this indolamine might be dependent on the species or tissue type[10,11]. However, the number of works is small, requiring further research in this field.

In a study that included 210 patients with chronic renal failure who underwent kidney transplantation[10],

TABLE 1. EFFECTS OF ORGAN TRANSPLANTATION PROCEDURE ON SERUM MELATONIN LEVEL

Author/year	Species	Groups	Objective	Method	Results
Viljoen et al.[10], 1992	Humans (n=210)	Control group (n = 35); Experimental group (n=175)	Determine melatonin concentration after transplantation.	RIA Method	Drop in serum melatonin levels after transplantation
Cardell et al.[11], 2008	Rats	Control group (n=6); Experimental group 1 (n=6); Experimental group 2 (n=6); Experimental group 3 (n=6)	Determine melatonin concentration after transplantation.	RIA Method	Transplant exposure did not affect serum melatonin concentration.

TABLE 2. EFFECTS OF MELATONIN ON THE TRANSPLANTED GRAFT

Author/Year	Species	Groups	Objective	Method	Results
Inci et al.[12], 2002	Rats	Control group (n=10); Experimental group (n=10)	To evaluate the protective effect of melatonin on transplantation	Biochemical and morphological analysis	Oxidative stress reduction
Jung et al.[13], 2004	Rats	Control group (n=12); Experimental group 1 (n=12); Experimental group 2 (n=8)	To evaluate the action of melatonin on acute transplant rejection.	RIA Method	Improved transplant
Santana-Rodríguez et al.[14], 2011	Rats	Donar group (n=25); Receiving Group (n=25); Control group (n=10); Experimental group 1 (n=5); Experimental group 2 (n=5); Experimental group 3 (n=5)	To evaluate the effect of melatonin on lung transplantation	Radiological, histological and inflammatory analysis	Improved transplant

this reduction was significant. In contrast, in the second study[11] conducted on rats, the authors observed that serum melatonin levels did not change significantly after the procedure of heart transplant in rats. The effect of surgical stress on melatonin reduction has been reported in other studies[16] and reinforces the result found in patients with renal failure[10]. Besides, the very clinical conditions of patients with renal failure and transplantation may have influenced an increase in melatonin clearance[10]. Therefore, greater elimination could occur than a fall in production. Regarding the second study, the number of animals employed is small, which would be the major limitation of this study[11].

Melatonin has a circadian cycle, regulated by the suprachiasmatic nucleus that receives information about the luminosity of the retinohypothalamic tract. Thus, melatonin production is higher at night and lower during the day[17]. Therefore, the time of blood collection may influence the interpretation of data[10,11]. Neither of the selected studies evaluated the melatonin curve, ie, several collections for 24 hours. This fact may have limited the studies.

Also, melatonin is produced in leukocytes and other tissues[18] that may have interference from immunomodulatory substances or suppressors employed in kidney transplantation. Two immunosuppressants were used in the renal transplant study: calcineurin inhibitor and rapamycin blocker (mTOR). The first drug increased serum melatonin levels, and the second led to a reduction in melatonin levels. Therefore, besides the stress of the surgical procedure, the type of immunosuppressant can negatively impact melatonin production[10].

In general, studies on the effects of melatonin on organ transplants had a positive effect on graft: a) reduction of oxidative stress; b) fall of the inflammatory process; c) decreased apoptosis; d) less rejection; e) longer survival of animals[12-14]. However, the concentration of melatonin employed was high in all studies[12-14], which may result in a serum concentration of this supraphysiological hormone[19], which may be a limitation in the interpretation of the data. It seems that the effect of melatonin may be dose-dependent, according to the study by Jung et al.[13].

The study by Santana-Rodríguez et al.[14] compared the effects of melatonin with those of estrogens, which may have a proliferative effect on tissues. In this study, the authors found the highest survival of animals using melatonin and the lowest with estradiol. Possibly, the properties of melatonin may help slow the graft rejection process, which has a direct impact on animal survival. In in vitro studies, estradiol may decrease melatonin receptor expression[20,21]. This fact may explain the result of greater graft rejection in the estrogen-treated group.

The limitations of this systematic review are the small number of studies with adequate methods to evaluate the relationship between melatonin and organ transplantation. This fact made the meta-analysis impossible. Also, there is a need for studies on the long-term effect of grafts in animal models. The strongest point of this review is the fact that melatonin may decrease graft rejection in animal models. This may be the future clinical application of melatonin. However, further studies are needed, especially in patients undergoing organ transplantation to assess their safety.

CONCLUSION

Our results suggest that serum melatonin concentration may be affected by the surgical procedure of kidney transplantation, as well as by the type of immunosuppressive therapy employed. In addition, the use of high-dose melatonin decreases graft rejection due to melatonin's antioxidant and anti-inflammatory properties.

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Statement

The authors do not have any conflict of interest.

Author's contributions

CFH - Made substantial contributions to the concept and design of the study, and definition of intellectual content; was involved in literature search, data analysis, statistical analysis, and manuscript preparation; in drafting the article or revising it critically for important intellectual content; gave final approval to the version to be published.

JMH - Made substantial contributions to the concept, design of the study, and definition of intellectual content; was involved in literature search, data analysis, statistical analysis, and manuscript preparation; in drafting the article or revising it critically for

important intellectual content; and gave final approval to the version to be published.

ECAV - Was involved in data analysis and statistical analysis; in drafting the article or revising it critically for important intellectual content; and gave final approval to the version to be published.

ICES - Was involved in data analysis and statistical analysis; in drafting the article or revising it critically for important intellectual content; and gave final approval to the version to be published.

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RCC - Was involved in data analysis and statistical analysis; in drafting the article or revising it critically for important intellectual content; and gave final approval to the version to be published.

ECB - Made substantial contributions to the concept, design of the study, and definition of intellectual content; was involved in the manuscript preparation; drafting the article or revising it critically for important intellectual content, and gave final approval of the version to be published.

JMSJ - Made substantial contributions to the concept, design of the study and definition of intellectual content; was involved in manuscript preparation; drafting the article or revising it critically for important intellectual content, and gave final approval of the version to be published.

RESUMO

A melatonina tem propriedades anti-inflamatórias e antioxidantes que podem influenciar o crescimento e a apoptose dos tecidos. Esse aspecto pode influenciar o sucesso do transplante de órgãos.

OBJETIVO: *Avaliar a relação entre a melatonina e o transplante de órgãos.*

MÉTODO: *A revisão sistemática foi realizada nas bases de dados do PubMed, usando os termos de pesquisa: "fisiologia da melatonina" ou "terapêutica da melatonina" e "farmacologia do transplante" ou "fisiologia do transplante" ou "terapêutica do transplante" ou "terapia do transplante". Não foram incluídos os experimentos sobre os órgãos do sistema reprodutivo. Após análise, cinco artigos foram selecionados após a leitura do título e do resumo de 50 manuscritos. Os trabalhos foram divididos em duas vertentes: a) análise da influência do procedimento de transplante de órgão na produção de melatonina; b) ação da melatonina sobre o transplante de órgãos.*

RESULTADOS: *O procedimento cirúrgico do transplante cardíaco, a imunossupressão e o enxerto não influenciaram a secreção de melatonina em roedores, mas houve redução significante da melatonina nos casos do procedimento de transplante renal em pacientes com insuficiência renal. A ministração de melatonina em modelos experimentais diminuiu a rejeição e melhorou o sucesso de transplante.*

CONCLUSÃO: *Os estudos mostram que a melatonina pode reduzir a dependência da espécie e do órgão e que o emprego da melatonina diminui a rejeição do órgão.*

PALAVRAS-CHAVE: *Melatonina. Estresse oxidativo. Transplantes.*

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