Potential benefits of melatonin in organ transplantation: a review

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Abstract

Organ transplantation is a useful therapeutic tool for patients with end-stage organ failure; however, graft rejection is a major obstacle in terms of a successful treatment. Rejection is usually a consequence of a complex immunological and nonimmunological antigen-independent cascade of events, including free radical-mediated ischemia-reperfusion injury (IRI). To reduce the frequency of this outcome, continuing improvements in the efficacy of antirejection drugs are a top priority to enhance the long-term survival of transplant recipients. Melatonin (*N*-acetyl-5-methoxytryptamine) is a powerful antioxidant and ant-inflammatory agent synthesized from the essential amino acid ʟ-tryptophan; it is produced by the pineal gland as well as by many other organs including ovary, testes, bone marrow, gut, placenta, and liver. Melatonin has proven to be a potentially useful therapeutic tool in the reduction of graft rejection. Its benefits are based on its direct actions as a free radical scavenger as well as its indirect antioxidative actions in the stimulation of the cellular antioxidant defense system. Moreover, it has significant anti-inflammatory activity. Melatonin has been found to improve the beneficial effects of preservation fluids when they are enriched with the indoleamine. This article reviews the experimental evidence that melatonin is useful in reducing graft failure, especially in cardiac, bone, otolaryngology, ovarian, testicular, lung, pancreas, kidney, and liver transplantation.

Key Words
▸ melatonin
▸ organ transplantation
▸ graft failure
▸ ischemia-reperfusion injury
▸ preservation fluids

Introduction

Organ transplantation is a useful therapeutic tool for patients with end-stage organ failure. Surgery, drugs, and knowledge innovations may possibly improve results allowing this procedure to be used for other organs. According to World Health Organization (WHO), 114,690 transplants were performed worldwide in 2012, 1.8% more than in 2011, but still less than 10% of the global needs. Kidney (68%) and liver (21%) are the most frequently transplanted organs, and more of them are from deceased donors (58% kidney and 82% liver) (http://www.transplant-observatory.org accessed 24 September 2015). Continuing improvements in the efficacy of antirejection drugs have greatly contributed toward prolonging the long-term survival of transplant recipients; however, the 5-year survival following transplantation remains low (90% for renal, 75% for heart, 72% for liver, 55% for lung, and only 50% for heart–lung) (Fildes *et al.* 2009).

Moreover, lifelong use of immunosuppressive drugs increases the risk of opportunistic diseases and malignancies. About 20% of transplanted patients have a diagnosis of cancer after 10 years of continued immunosuppressive therapies, a risk two- to five-fold higher than that of the general population (Vajdic *et al.* 2006).

Complex immunological and nonimmunological problems accompany organ graft failure. A nonimmunological antigen-independent cascade of events is produced by ischemia-reperfusion injury (IRI). IRI is a pathological condition characterized by an initial restriction of blood supply to an organ followed by the restoration of perfusion, which involves oxidative stress that arises from the imbalance between free radical overproduction and insufficient antioxidant defense (Witzigmann *et al.* 2003, Land 2005). This process leads to cell death through the activation of several pathways (Selzner & Clavien 2001, Yellon & Hausenloy 2007, Ben Mosbah *et al.* 2010).

Melatonin (*N*-acetyl-5-methoxytryptamine) is a powerful antioxidant (Tan *et al.* 1993, Rodriguez *et al.* 2004, Zhang & Zhang 2014, Galano *et al.* 2015, Manchester *et al.* 2015) produced by the pineal gland as well as by many other organs including ovary, testes, bone marrow, gut, placenta and liver (Tan *et al.* 1999, Venegas *et al.* 2012, Acuña-Castroviejo *et al.* 2014, Reiter *et al.* 2014). It is synthesized from the essential amino acid ʟ-tryptophan in a process mediated by the action of four enzymes: tryptophan hydroxylase, ʟ-aromatic amino acid decarboxylase, *N*-acetyltransferase, and acetylserotonin methyltransferase (Singh & Jadhav 2014). Melatonin is a biological rhythm regulator and has a variety of other essential functions (Hardeland *et al.* 2009, Reiter *et al.* 2009*a*, 2013, Maria & Witt-Enderby 2014, Romero *et al.* 2014, Coelho *et al.* 2015, Vriend & Reiter 2015).

A strong immunogenic stimulus of an allogeneic solid organ transplant does not modulate the endogenous patterns of melatonin secretion (Cardell *et al.* 2008). For this and other reasons, and the fact that melatonin supplementation is considered safe, without reported adverse events (Buscemi *et al.* 2006), we suggest that melatonin would have beneficial effects in organ transplantation. We initially explain the graft rejection processes and thereafter provide the rationale for the proposed use of melatonin.

Ischemia-reperfusion injury

Cold ischemia causes parenchymal cell death as a consequence of widespread cellular metabolic disturbances resulting from glycogen consumption, lack of adequate oxygen supply, ATP depletion, and degradation of ATP into its metabolites (adenosine, inosine, and hypoxanthine), the conversion of xanthine oxidase by xanthine dehydrogenase, and reduced intracellular pH (Teoh & Farrell 2003, Zhai *et al.* 2011). The decrease in pH levels is accompanied by lowered mitochondrial oxidative phosphorylation (Kanoria *et al.* 2012). There is also reduced vascular perfusion, which is caused by endothelial swelling, intravascular hemoconcentration, and an imbalance between the vasoactive mediators endothelin (ET) and nitric oxide (NO·) (Kukan & Haddad 2001, Scheinichen *et al.* 2003, Ramalho *et al.* 2006).

Reperfusion injury involves both direct and indirect cytotoxic mechanisms including an inflammatory immune response with the release of inflammatory mediators; interleukins (ILs) and TNF-α cause oxidative stress injury and recruitment of leukocytes (Lutz *et al.* 2010, Zhai *et al.* 2011). These processes are summarized in Fig. 1. In addition, during vascular reperfusion, ATP metabolites are produced with increases in reactive oxygen species (ROS) levels including superoxide radical (O_2^{--}), hydrogen peroxide (H_2O_2), and the hydroxyl radical (·OH) (Boros & Bromberg 2006, Huang *et al.* 2007). The ·OH, which is produced due a reductive cleavage of H_2O_2 by Fe^{2+} or Cu^{2+}, initiates the process of lipid peroxidation (LPO), this process consists of a radical chain reaction that leads to the destruction of polyunsaturated fatty acids. LPO disrupts normal fluidity and permeability of cell membranes causing cell edema, massive overload of Ca^{2+} and Na^+, and cell lysis (Korkmaz *et al.* 2009, Negre-Salvayre *et al.* 2010). Malondialdehyde (MDA) and 4-hydroxynonenal (4-HNE) are produced during LPO and are indicators of ROS-dependent tissue damage. MDA promotes the activation of nuclear factor-κB (NF-κB) through an inflammatory process, which regulates the expression of proinflammatory cytokines. 4-HNE is a chemoattractant for neutrophils (Jaeschke 1996).

During LPO, mitochondrial membrane permeability is increased due to a loss of mitochondrial integrity. This occurs as a result of the depletion of ATP levels and a rise in cellular Ca^{2+} concentrations, which promote an overload in mitochondrial Ca^{2+}. This dysfunction results in the release of cytochrome *c* into the cytoplasm, subsequent activation of caspase activity, and initiation of apoptotic cell death (Crompton 1999). Changes in the permeability at mitochondrial membrane are mediated via activated pro-apoptotic members of the BCL2 family of proteins, including BAX or BAK (Reed 1994), or it is

secondary to mitochondrial permeability transition pore (MPTP) opening (Baines *et al.* 2005, Green 2005).

NO is generated by three different synthase isoforms (NOS): endothelial (eNOS), neuronal (nNOS), and inducible synthase (iNOS); each utilizes L-arginine and produces NO· and L-citrulline (Hines *et al.* 2002, Hsu *et al.* 2002). During IRI, diminished NO· levels are due to both decreased production and increased scavenging of NO· by elevated levels of ROS. This is important because NO· modulates the intensity of the IRI by regulating neutrophil adhesion and platelet aggregation (Serracino-Inglott *et al.* 2001). During IRI, endothelial dysfunction occurs including a reduction in eNOS function due to a direct action and the elaboration of the endogenous competitive inhibitors (asymmetric dimethylarginine, ADMA), the increased coupling of NO· with $O_2^{·-}$ (which generates the peroxynitrite anion, ONOO·– a nonradical reactant which is equally toxic as ·OH) and cell-free hemoglobin, and the oxidation of target soluble guanylyl cyclase, a molecular target of NO· (Li *et al.* 2014).

Melatonin greatly limits IRI based on its direct actions as a free radical scavenger as well as its indirect antioxidative actions in the stimulation of the cellular antioxidant defense system, that is, by increasing mRNA levels and activities of several important antioxidant enzymes (Barlow-Walden *et al.* 1995, Pablos *et al.* 1998); these include superoxide dismutase (SOD, which catalyzes the conversion of $O_2^{·-}$ to H_2O_2), glutathione peroxidase (GPx), glutathione reductase (GRd), and glutamylcysteine ligase, which promotes the synthesis of another important intracellular antioxidant, glutathione (GSH) (Reiter *et al.* 2000, Rodríguez *et al.* 2004, Hardeland 2005). In addition to directly scavenging several ROS and reactive nitrogen species (RNS), which are generated during IRI (Korkmaz *et al.* 2009, Reiter *et al.* 2010), it reduces myeloperoxidase (MPO) activity (Lee *et al.* 2002). Numerous studies have provided data showing that melatonin protects against the IRI-induced impairment of mitochondrial respiration, ATP synthesis, mitochondrial swelling, and LPO (Okatani *et al.* 2003, Kireev *et al.* 2013). Melatonin also reduces electron leakage from the respiratory chain that limits free radical generation and increases the expression of uncoupling protein, which is thought to improve electron flow through the respiratory chain and prevent mitochondrial $O_2^{·-}$ generation by increasing proton flow into the matrix (Pappolla *et al.* 1999, Jiménez-Aranda *et al.* 2013).
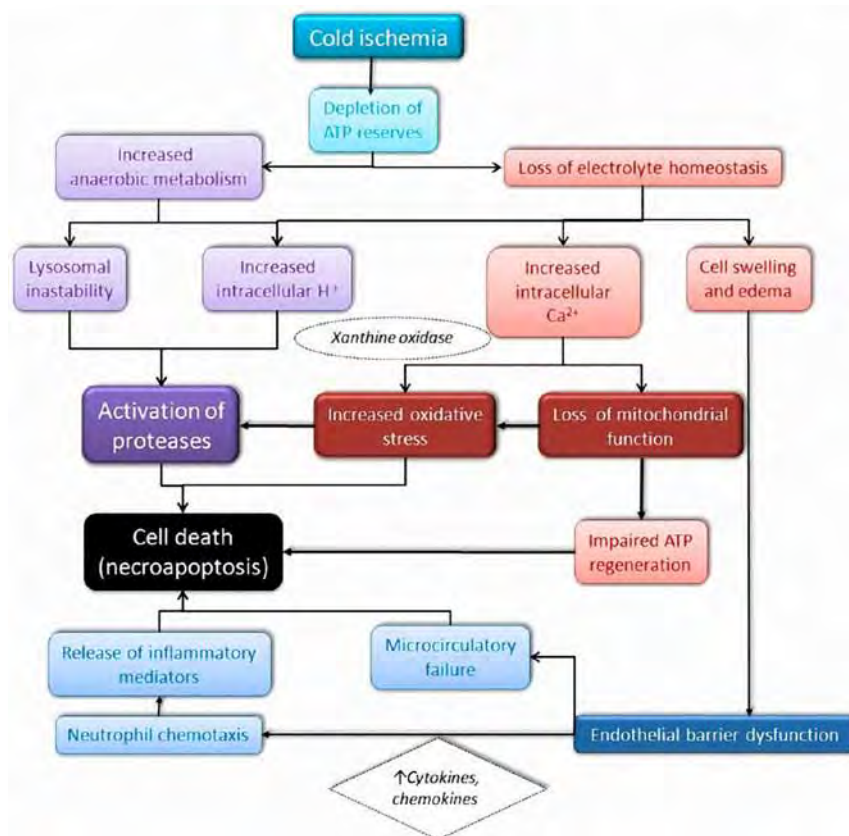
Figure 1

Liver IRI physiopathology. Cold ischemia induces cellular ATP depletion, which results in the loss of electrolyte homeostasis and increases anaerobic metabolism promoting intracellular Ca^{2+} and H^+ accumulation and lysosomal instability. These events inhibit mitochondrial oxidative phosphorylation, thereby reducing ATP synthesis and activating proteases. Perturbations of electrolyte homeostasis generate cellular swelling and edema, which result in narrowing of the sinusoidal lumen and microcirculatory dysfunction via endothelial barrier dysfunction. These alterations contribute to organ neutrophil accumulation through the induction of neutrophil chemoattractants and adhesion molecules. Neutrophil extravasation generates parenchymal injury due to the production of ROS. Finally, cell death culminates in necrosis or apoptosis depending on the decline of cellular ATP (major degradation and no regeneration causes necrosis). A full colour version of this figure is available at http://dx.doi.org/10.1530/JOE-16-0117.

Melatonin also regulates the activity of a marker of mitochondrial membrane integrity that is reduced during IRI: mitochondrial glutamate dehydrogenase (GDH). Moreover, melatonin stabilizes microsomal membranes, enabling them, in a concentration-dependent manner, to resist the rigidity induced by free radical attack (García *et al.* 2014). Additionally, melatonin suppresses the cytochrome *c* released into the cytoplasm due to mitochondrial swelling (Kim & Lee 2008).

Finally, melatonin also preserves the functional and energetic status of cells during IRI by reducing concentrations of TNF-α (a pleiotropic cytokine generated by numerous cell types in response to various inflammatory and immunomodulatory stimuli) and inhibiting iNOS expression and NO· production. Melatonin augments the rise in *eNOS* mRNA levels, whereas it reduces the elevation of *iNOS* mRNA levels (Rodriguez-Reynoso *et al.* 2001, Kilic *et al.* 2005, Wang *et al.* 2005). This is important because eNOS-derived NO· is suggested to be an important protective factor against vascular endothelium pathophysiology because it is produced early and may abrogate the microcirculatory stress of engraftment and reperfusion. Conversely, iNOS-derived NO· promotes ischemic injury by increasing free radical formation since it is generated several hours after

stimulation and its production is not beneficial at this later time (Albrecht *et al.* 2003, Shah & Kamath 2003). Some of the numerous processes by which melatonin functions as a direct free radical scavenger and indirect antioxidant are summarized in Fig. 2.

Preservation solutions

Preservation solutions play an important role in maintaining tissues for transplantation; these fluids have been subjected to numerous tests based on changes in ionic composition and in the inclusion of molecules designed to reduce intracellular and interstitial edema. During cold ischemia, sodium–potassium (Na^+/K^+) ATPase is inhibited elevating Ca^{2+} concentrations. This disturbance generates a local rise in intracellular osmolarity and edema and loss of membrane cell elasticity (Lang *et al.* 1995). To prevent this, a preservation solution including high-K^+ levels was examined, but not found to be useful because of the generated blood vessel constriction (Ramella-Virieux *et al.* 1997). The addition of 'impermeants' such as mannitol, raffinose, glucose, lactobionic acid, and gluconate or high Na^+ concentration was also not beneficial because these constituents diffused into the
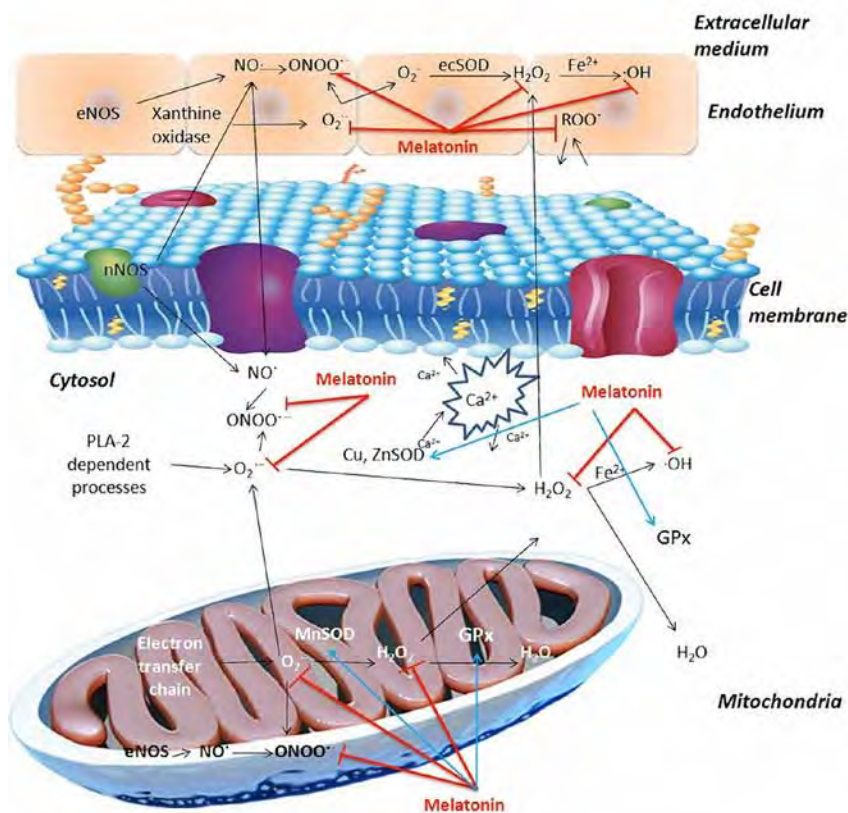
Figure 2
Melatonin's direct (red) an indirect effects (blue). In the endothelium, xanthine oxidase generates O_2^- degrading xanthine to hypoxanthine; melatonin and its metabolites are scavengers of this and other ROS. Melatonin, in the extracellular medium and mitochondria, is also a scavenger of $ONOO^-$ generated as a result of the availability of NO· due to eNOS and nNOS activity. Furthermore, O_2^- reactions with extracellular superoxide dismutase (ecSOD) give rise to H_2O_2, which suffers a reduction with Fe^{2+} generating ·OH. Melatonin neutralizes these ROS. In the cytosol and mitochondria, similar processes occur with the action of MnSOD and Cu/ZnSOD. Glutathione peroxidase (GPx) reduces H_2O_2 to H_2O and O_2. Melatonin increases the activity of this enzyme and also the activity of SOD, which are important antioxidant enzymes. During IRI, a depletion of ATP occurs and an increase in intracellular Ca^{2+} develops, which increases oxidative stress and loss of mitochondrial function. eNOS, endothelial nitric oxide synthase; H_2O_2, hydrogen peroxide; iNOS, inducible nitric oxide synthase; NO, nitric oxide; PLA-2, phospholipase A2; ROO·, alkyl peroxyl radical; O_2^-, superoxide radical; ·OH, hydroxyl radical; $ONOO^-$, peroxynitrite. A full colour version of this figure is available at http://dx.doi.org/10.1530/JOE-16-0117.

interstitial medium and caused edema. Thereafter, it was observed that macromolecules called 'colloids' (albumin (Alb), hydroxyethyl starch, polyethylene glycol, and dextran) generate high oncotic pressure and the addition of these to solutions with low Ca^{2+}, high Na^+, and carefully adjusted K^+ and magnesium (Mg^{2+}) concentrations solved the problems observed earlier (Southard 1997).

University of Wisconsin solution (UW), Institute Georges Lopez solution (IGL-1), Celsior (CE) solution, Euro-Collins solution, and histidine–tryptophan–ketoglutarate solution (HTK) are the most frequently used preservation solutions (Table 1). Euro-Collins solution was the first used, which does not contain oncotic agents but does contain glucose (impermeable to renal cells for short time but not in liver and pancreatic cells causing anaerobic metabolism of glucose and inducing intracellular acidosis) (Bejaoui *et al.* 2015).

It is presumed that preservation solutions with lower viscosity (like HTK) may improve graft survival (Puhl *et al.*

Table 1 Composition of cold storage solutions for organ preservation.

	UW	CE	HTK	IGL-1	Euro-Collins
Osmolarity (mOsm/L)	320	320	310	320	375
pH	7.4	7.3	7.2	7.4	7.1
Viscosity (cp)	5.70	1.15	1.8	1.28	N/A
Na^+ (mmol/L)	25–30	100	15	120	10
K^+ (mmol/L)	125–130	15	10	30	115
Mg^{2+} (mmol/L)	5	13	4	5	–
Ca^{2+} (mmol/L)	–	0.25	0.015	–	–
Cl^- (mmol/L)	–	41.5	50	20	15
PO_3^- (mmol/L)	25	–	–	25	47.5
SO_4^- (mmol/L)	5	–	–	5	30
HCO_3^- (mmol/L)	–	–	–	–	10
Glucose (mmol/L)	–	–	–	–	195
Histidine (mmol/L)	–	30	198	–	–
Tryptophan (mmol/L)	–	–	2	–	–
Glutamate (mmol/L)	–	20	–	–	–
α-Ketoglutarate (mmol/L)	–	–	1	–	–
Lactobionate (mmol/L)	100	80	–	100	–
Mannitol (g/L)	–	60	30	–	–
HES (g/L)	50	–	–	–	–
PEG-35 (g/L)	–	–	–	1	–
Raffinose (mmol/L)	30	–	–	30	–
Adenosine (mmol/L)	5	–	–	5	–
Allopurinol (mmol/L)	1	–	–	1	–
Glutathione (mmol/L)	3	3	–	3	–

Additional ingredients in UW are penicillin G, insulin, and dexamethasone. Viscosity data refer to a temperature of 4°C. From Petrowsky and Clavien (2014) and Adam *et al.* (2015).CE, Celsior solution; cp, centipoises; HES, hydroxyethyl starch; HTK, histidine–tryptophan–ketoglutarate solution; IGL-1, Institute Georges Lopez solution; PEG-35, polyethylene glycol 35 kDa; UW, University of Wisconsin solution.

2006). It was also found that antioxidants and protective molecules such as polyethylene glycol 35 kDa (PEG-35) in IGL1 solution and hydroxyethyl starch (HES) in UW solution improved the efficiency of the solutions and consequently graft survival. HTK solution is less effective because its composition is poor in these agents (Belzer & Southard 1988).

Yang and He (2005) reviewed the data related to the use of preservation solutions in cardiac transplantation. The authors noted that UW was an effective tissue protector in heart transplantation (Swanson *et al.* 1988), but less effective in abdominal-tissue transplantation. This was because cardiac cells can only be preserved for 4–6 h, while abdominal organs must be preserved for 24–48 h (Stringham *et al.* 1992). HTK solution is also observed to be effective by restricting the tissue acidosis induced by ischemia (Reichenspurner *et al.* 1993, Gu *et al.* 1996). In addition, some studies confirmed the efficacy of Celsior solution in reducing IRI (Menasché *et al.* 1994). Moreover, the authors observed that NO, hyperkalemia, and IRI made transplant outcomes worse, while Mg^{2+} and endothelium-derived relaxing factor attenuated these effects.

Pancreatic preservation fluids also have been studied. It is observed that UW produced results similar to those of HTK (Salehi *et al.* 2006) and better outcomes than Celsior solution (Hubert *et al.* 2007). For kidney transplantation, the UW solution provides good results in short- and long-term tissue preservation (Xiaodong & Ashok 2010, Catena *et al.* 2013). IGL1 exhibits similar positive outcomes as UW (Codas *et al.* 2009) or even better (Badet *et al.* 2005).

Donderó *et al.* (2010) and Adam *et al.* (2015), in a liver transplantation review, summarized the data related to the utility of UW solution and IGL1 solution to resist graft rejection. A slight graft rejection increase with CE solution and a significant reduction with HTK solution was observed. Moreover, the authors observed that HTK caused major graft rejections and constitutes an independent risk factor compared with UW, which increased the probability of graft loss by 10%. These results were also previously reported (Mangus *et al.* 2008, Stewart *et al.* 2004). Similar results were observed when CE and IGL1 were compared. Moreover, in partial grafts, IGL1 provided better survival than the other solutions because it increased the mediators that promote liver regeneration such as AMP-activated protein kinase (AMPK) (Bouma *et al.* 2010). Furthermore, UW and IGL1 solutions enriched with trophic factors, such as epidermal growth factor and insulin-like growth factor-1, are observed to enhance the resistance of steatotic livers

to IRI, partly due to protein kinase B (PKB) and eNOS signaling activation, and reduced cytokine release (Zaouali *et al.* 2010*a*,*b*).

Attending to cardiac transplantation, preservation fluids also play a pivotal role in graft survival. A solution consisting of melatonin (100 mmol/L), adenosine (400 µmol/L), lidocaine (1000 µmol/L), and insulin (0.01 IU/mL) was compared with adenosine-lidocaine cardioplegia with low Ca^{2+}/high Mg^{2+} concentration levels, HTK solution, and Celsior solution (Rudd & Dobson 2011). The authors observed a higher recovery of aortic flow and coronary flow by using the melatonin preservation solution compared with other treatments. Heart rate and systolic pressure were also better in this group. In addition, lactate levels were lower in these animals, and troponin values were not detected after 5 min of reperfusion, as observed in the adenosine-lidocaine-treated rats.

Preservation solutions also play an important role in kidney transplantation. Melatonin added to UW solution decreases significantly MDA and lactate dehydrogenase (LDH) more than UW solutions without melatonin in transplanted kidneys (Aslaner *et al.* 2013).

In liver transplantation, adding melatonin at a concentration of 100 µM in Krebs–Henseleit bicarbonate (KHB) solution and added to UW and Celsior solutions attenuates the histopathological effects produced during IRI of hepatocytes (Freitas *et al.* 2006). LDH and GSH levels of melatonin-treated rats were similar to control values. ATP levels were restored by melatonin after IRI; these values are usually reduced seven-fold. These results are in agreement with previous studies (Vairetti *et al.* 2005), but in this case a dose-dependent effect of melatonin on bile production and biliary bilirubin secretion also was observed. ATP levels were likewise increased and GGT levels reduced. GSH and LDH did not exhibit any modifications. These benefits were better when melatonin was added to the UW solution than to the Celsior solution.

The ubiquitin proteasome system (UPS) is an energy-dependent system that degrades misfolded proteins and regulates various cellular processes (Padrissa-Altés *et al.* 2012). In liver, it has been recently demonstrated that the addition of the reversible UPS inhibitors bortezomib (BRZ) and carbobenzoxy-Leu-Leu-leucinal (MG132) to UW solution improved steatotic and nonsteatotic liver preservation, and that the protective effect of BRZ was superior to that of MG132 (Zaouali *et al.* 2013*a*). IGL1 solution supplemented with BRZ also showed protective effects which were partially mediated through the activation of AMPK and Akt/mTOR signaling (Bejaoui *et al.* 2014). Melatonin has similar actions to BRZ, which could contribute to the ability of melatonin to protect transplanted tissues (Vriend & Reiter 2014*a*,*b*).

Organ transplantation

Cardiac transplantation

Cardiac transplantation is a useful treatment for patients with end-stage heart failure or severe coronary arterial disease (Gill 2008). The outcome of these procedures have improved using cyclosporine (CsA) as an immunosuppressive therapy (Aumente *et al.* 2005), but this drug has several limitations due to its side effects (Baan *et al.* 1994). Melatonin has been studied as an agent to protect against graft rejection.

In a rat model using Thomas solution with melatonin (0.1 mmol/L) (Gao *et al.* 2003), cardiac functional recovery, coronary vasodilatory response to acetylcholine chloride, and myocardial high energy phosphate findings, were much better than those of control animals after 12 h of hypothermic ischemia. Furthermore, creatine kinase (CK) levels were lowered in treated group after 15 min of reperfusion. In addition, degeneration, swelling, and loss of normal dense granules in mitochondria were observed in non-melatonin-treated animals, but not in treated rats. These results are in agreement with another study where melatonin was given orally suspended in 1.5 mL saline solution (one group received 20 mg/kg and another group 200 mg/kg melatonin) (Jung, *et al.* 2004). The authors observed a prolonged allograft survival in the melatonin-injected animals (7.3 ± 1 and 12.3 ± 1 days, respectively) versus control rats (6.3 ± 1 days) due to a decreased proliferative capacity of recipient lymphocytes and due to a reduction in the synthesis of allospecific antibodies.

Melatonin also produced beneficial effects in cardiac transplantation through a synergetic action with CsA in a rat model (Liu *et al.* 2014). The authors administered 200 mg/kg/day of melatonin to one group, 20 mg/kg/day of CsA to the second group, and 50 mg/kg/day of melatonin with 5 mg/kg/day of CsA to the third group. CsA was more effective than melatonin alone on graft survival, but combining these drugs gave the best result (31.6 ± 2.4 days). This finding may have been a result of a reduction in the expression of *P65*, *Bcl2*, and *Il1*β, which are key genes in inflammation and apoptosis. Histopathological data showed a similar release of inflammatory cytokines, including IL2 and TNF-α, and

cell apoptosis in melatonin and CsA group. However, the addition of these drugs produced an important decrease in heart congestion and cell survival. The results suggest that melatonin may be effective in prolonging cardiac allograft survival and reducing the dose of CsA, thereby reducing the side effects of the drug.

Bone transplantation

Melatonin is observed to be a promoter of bone formation *in vivo,* enhancing both the proliferation and differentiation of osteogenic cells (Takechi *et al.* 2008). Moreover, the indoleamine may increase gene expression of bone sialoprotein as well as other proteins and bone markers reducing the osteoblast differentiation period (Roth *et al.* 1999). Also, melatonin interferes with osteoclast activity, which is enhanced due to free radical actions. Melatonin limits the suppression of bone resorption due to its ability as a free radical scavenger (Koyama *et al.* 2002) and by downregulating nuclear factor B-mediated osteoclast activation (Ostrowska *et al.* 2010).

Pinealectomy generates spinal deformities due to the reduction in melatonin (Turgut *et al.* 2003). The authors also observed a reduction in the number of chickens with scoliosis with an enhanced values of Cobb angle and rib-vertebra value in pineal-transplanted birds versus pinealectomized chicks. The differences were not statistically significant between both groups, whereas significantly larger than those found in control group. Serum melatonin levels were depressed after pinealectomy, but pineal-transplanted animals were observed to have increased levels of melatonin, but the differences were also not statistically significant. Due to that, the authors conclude that the role of melatonin in the development of spinal deformity in chickens after pinealectomy remains controversial.

In a tibia rabbit model, melatonin (1.2 mg lyophilized powdered melatonin applied topically) added to a porcine bone graft was shown to improve new bone formation and cortical bone length compared with control animals or porcine bone alone at 15, 30, 45, and 60 days post-transplantation (Calvo-Guirado *et al.* 2015). These effects were the result of an increase in osteoblast proliferation in the peri-implant zone with an accelerated cell differentiation of the osteoid matrix. Melatonin's beneficial effects were observed radiographically and related to the Ca^{2+} levels, which were higher in melatonin-treated animals than in other groups. These results were statistically significant at 15 and 30 days post-transplantation.

Otolaryngology transplantation

Subtotal and total ear reattachment is a difficult surgery with a poor graft survival (Grabb & Dingman 1972). It has been shown that methylprednisolone sodium, dimethylsulfoxide, chlorpromazine, and indomethacin significantly improve survival of reimplanted auricular cartilage grafts in rabbits (Aden & Biel 1992, Henrich *et al.* 1995). Melatonin's benefits during auricular transplantation (500 mg/kg i.p.) were compared in a rat model versus dimethylthiourea (DMTU) and hyperbaric oxygen (HBO) (Lim *et al.* 1999). Template weights showed a significant improvement in graft survival with all treatments at days 7, 14, and 21. However, during photographic analysis, significant differences in graft survival were only found at day 7. Moreover, DMTU was the most effective treatment and HBO the worst.

Ovarian grafts

CsA has been used for several years to inhibit the recipient immune reaction during ovarian transplantation, but there is an important toxicity following its use (Ergüder *et al.* 2005). Thus, antioxidants including DMSO, 1,2-propanediol (PROH) (Abir *et al.* 2009), and vitamin E (Nugent *et al.* 1998) were used with beneficial effects in ovarian graft survival. Melatonin is known to be involved in ovarian physiology including follicular development, ovulation, oocyte maturation, and luteal function (Adriaens *et al.* 2006; Reiter *et al.* 2009*b*, Tamura *et al.* 2009). Furthermore, endometriosis is observed to be favored in pinealectomized rats with decreased levels of SOD and CAT activities and elevated MDA concentrations (Koc *et al.* 2010). Because of this and the antioxidant capacities of melatonin, its metabolites (Alvarez-Diduk *et al.* 2016) have been studied to prevent ovarian graft rejection.

Melatonin at doses of 20, 50, 100, and 200 mg/kg/day i.v. were used in a rat model to improve ovarian graft survival (Hemadi *et al.* 2012). With doses of 20 or 50 mg/kg, melatonin increased IL2 and interferon (IFN)-γ levels. However, at higher doses, the authors observed significant reductions of these cytokines. IL10 levels were also decreased using 100 and 200 mg/kg of melatonin. By comparison, IL4 levels were not changed when using the drug. Relative to allospecific serum antibodies (IgM, IgG, IgG1a, and IgG2a), the authors only founded significant benefits using 100 and 200 mg/kg of melatonin with a drop in IgM and IgG2a levels compared with control values. However, at the morphological level, these higher doses

did not appear to be beneficial. Apoptosis of primordial follicles also followed melatonin administration. There were no healthy antral follicles in the vitrified thawed ovaries treated with melatonin 6 days after transplant, but they did reappear at the seventh day after transplantation in both nontreated and most melatonin-treated ovaries.

Melatonin (20 mg/kg i.p.) also was compared with oxytetracycline (10 mg/kg i.p.) in an autologous intraperitoneal ovary transplantation system in rats (Sapmaz *et al.* 2003). Melatonin was statistically significantly more effective in reducing ovarian necrosis and tissue MDA levels than was oxytetracycline. The indoleamine (240 mg/L orally) was also compared with hyaluronan (HA), vascular endothelial growth factor A (VEGF-A) (200 ng/mL), and vitamin E (400 IU/mL) in a human ovarian material study after its transplantation into immunodeficient mice (Friedman *et al.* 2012). The authors observed a reduced apoptosis in all treated animals, but these results were statistically significant in melatonin + HA-rich biological glue + VEGF-A + vitamin E animals. There were no significant differences in VEGF-A expression among the tissues. Atretic follicles were significantly higher in the untreated animals than in the treated groups.

Testicular grafts

Spermatogenesis is disrupted during radiotherapy or chemotherapeutic treatment and the freezing of semen before treatment is the principal means of solving this problem (Lass *et al.* 2001, Agarwal & Allamaneni 2005). This treatment is obviously not useful for children, and about 2% of all malignant cancers occur during childhood and infancy (Brougham & Wallace 2005). Leydig cells and Sertoli cells are known to have receptors for melatonin and it has been suggested that melatonin may play a role in the spermatogenesis process (Frungieri *et al.* 2005).

Testicular grafts have been studied to promote spermatogenesis and melatonin is suggested to reduce transplant rejection rates. Hemadi *et al.* (2014), using a vitrified testicular graft model, observed that melatonin (20 mg/kg orally per day) reduces atrophic cords and improve preservation results of the morphological histology of the tissues than did nontreatment. These beneficial effects included a higher percentage of intact seminiferous tubules with ongoing spermatogenesis, reduced levels of activated myoid cells, decreased rate of lysosomes, phagolysosomes and lipid droplets in the Sertoli cells, more preserved Leydig cells, and a rise

in the number of mitochondria with well-developed cristae. The differences were statistically significant.

Spermatogonial cell transplantation into the testes of infertile animals was observed to lead to the reoccurrence of spermatogenesis (Orwig & Schlatt 2005, Mikkola *et al.* 2006, Kim *et al.* 2008). Melatonin treatment (20 mg/kg i.p. daily for 10 weeks after transplantation) was studied by Gholami *et al.* (2014) in a mice model. The results showed that large number of sperm was found in the lumen of seminiferous tubes with complete spermatogenesis in melatonin-treated animals. Furthermore, the morphological structure and the number of Leydig cells were also preserved. These results are in agreement with previous studies, where the administration of melatonin to azoospermic mice led to a complete regeneration of germ cells with the appearance of elongated and round spermatids (Mohammadghasemi *et al.* 2010).

Lung transplantation

Lung transplantation is an effective therapeutic option in the treatment of patients with end-stage pulmonary diseases. However, early acute graft dysfunction is a serious obstacle in obtaining a successful outcome due to significant postoperative morbidity and mortality (Hosepund *et al.* 1999). It is observed that IRI is a common complication after lung transplantation; this is characterized by nonspecific alveolar damage and pulmonary edema (De Perrot *et al.* 2003).

Inci *et al.* (2002) studied the IRI effects after lung transplantation and the ability of melatonin to prevent the damage in a rat model. Significantly higher oxygen blood levels 2 h after graft reperfusion was observed in melatonin-treated versus nontreated animals. Peak airway pressures and bronchoalveolar lavage nitrite values were also statistically significantly lower in treated animals. MDA levels generated by LPO and MPO activity were also significantly lower as a result of melatonin treatment.

Melatonin's beneficial effects against IRI after lung transplantation were also compared with other antioxidants including estradiol (25 mg/kg i.p.) and desferrioxamine (20 mg/kg i.p.) in a rat model (Santana-Rodríguez *et al.* 2011). The authors observed that melatonin (10 mg/kg i.p.) had similar effects to desferrioxamine in preventing IRI based on radiological evidence. However, estradiol treatment induced several complications, including moderate-to-severe edema. There were no significant differences between any treatment groups in terms of their efficacy against acute graft rejection.

CD26/dipeptidylpeptidase IV (CD26/DPP IV) is observed to modulate the biological effects of several chemokines, hematopoietic growth factors, neuropeptides, and hormones (Lambeir *et al.* 2003). As a result, it was predicted that this treatment may reduce IRI in lung transplantation (Jung *et al.* 2006, Zhai *et al.* 2007). The beneficial effects of this treatment against graft rejection were compared with melatonin (10mg/kg i.p.) in a rat model (Zhai *et al.* 2009). The authors observed a significantly poorer outcome in terms of graft survival after 7 days in melatonin-treated animals compared with those given CD26/DPP i.v. This study also reported an improvement of lung function and histological structure, decreased MDA levels, reduced MPO activity, and reduced vasoactive intestinal peptide levels, a neuropeptide involved in pulmonary parenchyma physiology with the latter treatment. These measures were statistically significant and were not investigated in the melatonin-treated animals.

Pancreas transplantation

Melatonin (10mg/kg/day/6 weeks) was shown to ameliorate type 2 diabetes mellitus associated with obesity due an increase of Ca^{2+} in muscle, liver, different adipose tissues, and pancreas in rats (Agil *et al.* 2015), and it reduced age-related insulin resistance in senescence-accelerated mice (Tresguerres *et al.* 2013). Moreover, blood levels of ghrelin, leptin, and melatonin are elevated in the initial phase of pancreatic inflammation, suggesting that these hormones could be a part of the innate resistance system against this condition. The exogenous administration of these substances produces a significant attenuation of severity of pancreatitis and protects pancreatic tissue from inflammatory damage. These beneficial effects are a result of inhibition of NF-κB, modulation of cytokine production, stimulation of heat shock protein (HSP), and the activation of the antioxidant system (Jaworek & Konturek 2014). As a result, melatonin also modulates pancreatic carcinogenesis through its direct and indirect actions and by increasing the efficacy of oncostatic drugs (Jaworek & Leja-Szpak 2014).

Once diabetes mellitus evolves, pancreas transplantation is an effective therapy, but technical failures and early graft failures due to loss of primary function are responsible for graft loss in 6–10% and 3–5% of the cases, respectively (Wullstein *et al.* 2004, Gruessner & Sutherland 2005). IRI is associated with alterations in mitochondrial function, which leads to the formation of oxygen-derived free radicals and LPO of the phospholipids in the cell membrane generating MDA

and 4-HDA (García-Gil *et al.* 2006, 2012); melatonin, in a rat model, reduces these degenerative changes (Muñoz-Casares *et al.* 2006). In addition, acute graft rejection is linked to a loss of organ function due to an increase in glucose concentrations and a reduction in membrane fluidity in pigs (García Gil *et al.* 2012).

There are few studies related of the ability of melatonin to prevent pancreas graft rejection. It has been observed that in nonobese diabetic (NOD) mice, melatonin (200mg/kg s.c.) prolongs pancreatic islet graft survival (Lin *et al.* 2009). The authors, however, did not observe differences of glucose or insulin levels in these animals. Melatonin decreased T helper 1 (Th1) cell levels, which play a pathogenic role during the initiation of the disease process. Consequently, melatonin reduced in a significant manner the proliferative capacity of recipient splenocytes due to a reduction in the expression of concanavalin A and CD3, which stimulates Th1. Furthermore, melatonin treatment significantly increased the population of IL10-producing CD4 T cells supporting their protective effects. The indoleamine also decreased the expression of cytokines (IFN-γ, TNF-α, IL4, IL1β, and TGF-β), but it did not influence systemic lymphocyte development. TNF-α results were only statistically significant.

The antioxidative effects of melatonin and ascorbic acid (AA) were compared in a pig transplantation model (García-Gil *et al.* 2011); both were given at 10mg/kg i.v. AA did not increase graft survival, while melatonin animals showed a significant rise in graft survival. This result was reflected in pancreatic function with better maintenance of normoglycemic status in the melatonin-treated pigs. Markers of LPO (MDA+4-HDA) were also decreased by both antioxidants, but the results were better in melatonin-treated pigs. Acute-phase protein/inter-α-trypsin inhibitor heavy chain 4 (pMAP/ITIH4), an acute protein observed during graft rejection, was only inhibited in pigs given melatonin. The authors did not report significant differences in amylase levels.

Kidney transplantation

Chronic kidney diseases lead to high oxidative stress markers and hemodialysis is not sufficient to adequately control these pathophysiologies (Pawlak *et al.* 2007). Like other organs, these conditions may benefit from organ transplantation and several studies observed changes in these markers after kidney transplantation (Simmons *et al.* 2005). The problem is that the inflammatory response generated by the graft implant may generate

oxidative stress and organ rejection (Vural *et al.* 2005, Barakat *et al.* 2010). Moreover, it is observed that diabetic patients have a further increase of oxidative markers due to their illness; this is associated with a poorer kidney allograft function (Morales-Indiano *et al.* 2009).

Several studies have tested antioxidants such as *N*-acetyl-cysteine (NAC) (Erdogan *et al.* 2006), vitamin C and E (Loong *et al.* 2004), and melatonin (Quiroz *et al.* 2008) in terms of their ability to reduce IRI. Melatonin (500 µg/kg) also provides protection against CsA-induced nephrotoxicity by decreasing blood urea, serum creatinine, and plasma MDA levels, and increasing creatinine and lithium clearance (Kumar *et al.* 1999). These disturbances are a result of oxidative stress injury. Similar protective antioxidant effects are observed against tacrolimus nephrotoxicity in a rat model; the protection by melatonin (4 mg/kg i.p.) is the result of its ability to modulate the increase of TNF-α, IL6, NO, and MDA levels (Ara *et al.* 2011). All results were statistically significant except those related to MDA levels.

Donor preconditioning with melatonin (50 mg/kg orally) was observed to prolong graft survival in a rat model of kidney transplantation (Li *et al.* 2009). Blood urea nitrogen (BUN), creatinine, transaminases, and LDH levels were increased in control animals after transplantation; melatonin reduced these levels significantly. The authors also observed that the indoleamine induced an elevation of tissue SOD while reducing lipid hydroperoxide levels. Melatonin also modulated the immune response by downregulating the expression of NF-κB p65, thereby modifying the activity of iNOS and caspase-3. In addition, a significant reduction in the histological damage of renal tubules was apparent.

Another problem observed after kidney transplantation is the disturbance in circadian rhythms and sleep–wake cycles including poor sleep quality, poor daytime functioning, and daytime sleepiness. These patients experience insomnia, restless legs syndrome (a neurological disorder), and obstructive sleep apnea (Burkhalter *et al.* 2015). It is suggested to be a result of an innate immune response (Kapsimalis *et al.* 2008, Besedovsky *et al.* 2012) or due to the inflammatory effects generated after transplantation (Castanon-Cervantes *et al.* 2010). A human multicenter study (Burkhalter *et al.* 2015) observed that the daytime bright light therapy improved sleep quality and the disorders derived from it. Decreased levels of melatonin were also observed in all patients, and the authors suggested that the intake of β-blockers and acetylsalicylic acid likely interfered with melatonin secretion, as shown in previous studies

(Brismar *et al.* 1988). However, melatonin levels in control subjects were similar to those in the intervention group, and behaviorally the patients showed significant statistical improvement as a result of melatonin. These results are in agreement with other studies (Russcher *et al.* 2015). In the latter case, the authors also did not observe beneficial effects on sleep quality due to melatonin-mediated improvement of renal function after transplantation; conversely, in an unpublished claim, kidney transplantation was associated with a rise of melatonin levels and an improvement in sleep quality due to the recovery of organ function (M Russcher, B C P Koch, C A J M Gaillard, J E Nagtegaal & P M Ter Wee, unpublished observations).

It is well known that a worst renal function is associated with sleep disorders (Ezzat & Mohab 2015). This may be a result of an imbalance between defensive agents (melatonin is decreased) and an increasing cell death rate due to the rise in oxidative markers such as TNF-α (Pinto *et al.* 2016). However, with improved renal function, low melatonin-related sleep disorders are observed to be reduced. More studies are clearly needed to define the circadian rhythm disturbances that accompany kidney transplantation.

Liver transplantation

Liver transplantation is the last-resort treatment for the end stage of both acute and chronic hepatic diseases. IRI, inherent in every liver transplantation process, is responsible of 81% of retransplantations during the first week after surgery due to poor function or primary nonfunction of the liver allograft (Belzer & Southard 1988, Shaw 1995). Graft failures are caused by prolonged cold storage, especially when steatosis is present. Also, donor fatty livers are associated with increased levels of recipient morbidity, mortality, and increased sensitivity to IRI (Chavin *et al.* 2004). This occurs because liver steatosis exhibits microvascular alterations, mitochondrial dysfunction, and a lower number of sinusoids, which increase IRI (Hui *et al.* 2004). Steatotic liver grafts are also associated with a primary nonfunction rate of 60% compared with less than 5% for nonsteatotic grafts (Selzner & Clavien 2001, Farrel *et al.* 2008).

During liver failure, ammonia levels may cause the arrhythmic release of melatonin from the pineal gland; this arrhythmicity is corrected after successful liver transplantation (Córdoba *et al.* 2009). However, whether these associations are real is questioned because it also suggested that hyperbilirubinemia (a pathological status

in liver failure patients) may interfere with the plasma melatonin assay (Middleton 2006).

AMPK activation during IRI leads to the stimulation of fatty acid oxidation and inhibition of lipogenesis, glucose production, and protein synthesis (Viollet *et al.* 2006). The activation of this enzyme produces the accumulation of α-subunit of hypoxia-inducible factor-1 (HIF1α, a transcription factor that functions as a master regulator of adaptive responses to reduced O_2 availability) (Fisslthaler & Fleming 2009) and induces NO· generation, which impairs the normoxic degradation of HIF1α (Zaouali *et al.* 2010*c*). In fatty livers, the combined effect of melatonin and trimetazidine (TMZ at 10^{-3} μM + melatonin 100 μM) as additives to IGL1 was observed to induce AMPK activation and enhance eNOS induction; as a consequence, HIF1α was stabilized (Zaouali *et al.* 2013*b*). The combination of drugs caused the activation of protective genes including *Hsp70*, *Bcl2*, erythropoietin, *Vegf*, and heme oxygenase-1 (*Ho1*) (Zaouali *et al.* 2013*a*). The benefits of the TMZ + melatonin cocktail added to IGL1 preservation solution in reducing endoplasmic reticulum stress and increasing autophagy in fatty liver grafts through the modulation of AMPK activity were also observed by other workers (Matsui *et al.* 2008, Wang *et al.* 2011).

The beneficial actions of melatonin were investigated by examining a pharmacological pretreatment cocktail, which included pentoxifylline (50 mg/kg intra-arterial), glycine (100 mg/kg intra-arterial), deferoxamine (30 mg/kg intra-arterial), NAC (150 mg/kg i.p.), erythropoietin (1000 IU i.p.), simvastatin (5 mg/kg intragastric), and melatonin (10 mg/kg i.p.) (von Heesen *et al.* 2011). The authors observed that the addition of melatonin induced a decrease of TNF-α and intercellular adhesion molecule 1 (ICAM1) levels (ICAM1 is induced by TNF-α and IL-1), with a significant attenuation of hepatic leukocyte infiltration, vacuolization, and cell death. This group also observed that with the multidrug treatment, MDA levels also lowered liver enzymes and excretory liver function levels were recovered to nearly control levels (von Heesen *et al.* 2012). These authors also used another multidrug treatment based on curcumin (50 mg/kg intragastric), simvastatin (5 mg/kg intrasgastric), NAC (150 mg/kg i.p.), erythropoietin (3000 IU/kg i.p.), pentoxyphylline (50 mg/kg i.p.), melatonin (10 mg/kg i.p.), glycine (100 mg/kg intra-arterial), and methylprednisolone 5 mg/kg intra-arterial (Moussavian *et al.* 2011). The significant increases of K+ (a cell membrane integrity marker), and ALT, AST, and LDH (parenchymal cell death indicators) were normalized by pretreatment with this cocktail. Furthermore, bile flow was restored and TNF-α, IL6, and MDA levels were reduced. These improvements

were in agreement with the histopathological findings, where a reduced vacuolization and caspase-3 expression was seen when melatonin was added to the cocktail.

Isolated primary human hepatocytes represent an alternative treatment to orthotopic liver transplantation (Smets *et al.* 2008, Fitzpatrick *et al.* 2009), and also a pathway to developing extracorporeal bioartificial livers (Allen *et al.* 2001). The problem is that during the isolation process, hepatocytes suffer IRI (Francés *et al.* 2007). A recent study (Solanas *et al.* 2015) used melatonin or DMSO to prevent this injury (perfusion with 5 mM melatonin compared with perfusion with 1% DMSO). These antioxidants produced similar cell viability and cell attachment results. Cellular dehydrogenase activity, urea and Alb levels, 7-ethoxycoumarin *O*-deethylase (a market of cytochrome P450 activity) activity were also increased by melatonin and were not statistical significant different from DMSO. The indoleamine was, however, better at decreasing LPO in hepatocytes than was DMSO.

Human dental pulp stem cells (hDPSCs) are observed to differentiate into hepatocyte-like cells (Ishkitiev *et al.* 2012). Because of this, a recent study tested the benefits of this treatment and melatonin (5 mg/kg i.p. twice a week) against liver cirrhosis (Cho *et al.* 2015). The authors observed a dose- and time-dependent relationship between melatonin and hepatic markers such as *Alb*, cytokeratin-18 (*Ck18*), CCAAT box enhancer-binding protein α (*C/Ebp*α), and hepatic nuclear factor-1α (*Hnf1*α). In addition, improvement of the immune response and a decrease of ALT, AST, and ammonia serum levels were also observed as a result of the addition of melatonin.

Conclusions

Melatonin's role preventing graft rejection and improving organ transplantation results have been studied principally in animal models. Nowadays, there are not many studies in human models. Therefore, it is impossible to confirm the indoleamine benefits in our species, but the results observed in animals are encouraging. In addition, we observed that melatonin dose used in organ transplantation is between 1000- and 3000-fold difference compared with melatonin dose for sleep and jet lag. Because of this difference of dosage, melatonin's pathway differs. In organ transplantation, the indoleamine effects are observed to be produced due to its free radical scavenger properties, while its benefits in sleep promotion and jet lag prevention are mediated

by melatonin action via indoleamine receptors (Laudon & Frydman-Marom 2014).

In conclusion, organ transplantation may be a useful therapeutic tool for the treatment of patients with end-stage organ failure. Outcomes of these procedures have been improved recently by using new solutions to prevent graft rejection allowing for a great variety of organs to be transplanted. IRI occurs during organ transplantation and melatonin may be protective because of the findings summarized herein. Furthermore, melatonin is effective in not only reducing graft rejection, but it also improves organ function during the post-transplant period. Melatonin's benefits are a result of its direct and indirect effects in cells. Moreover, melatonin is observed to increase the effectiveness of organ fluid preservation, which also plays a pivotal role in organ transplantation by reducing graft rejection. The observed results open a new advance for improvement of this important surgical technique. Additional studies would aid in defining additional mechanism to explain the beneficial actions of this endogenously produced and exogenously administered melatonin.

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