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Mini Review

Melatonin's Role in Preventing Graft Rejection in Steatotic Liver Transplantation, a Review

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Abstract

In both acute and chronic liver diseases, transplantation is the last-resort treatment. However, this treatment may fail due to an inherent process in organ transplantation, the ischemia-reperfusion injury (IRI). In fact, IRI is involved in 81% of re-transplantations during the first week after surgery due to primary non-function or poor function of liver allograft. These results are produced due to prolonged cold storage, especially if steatosis disease is preset. During cold IRI, steatotic livers exacerbate endoplasmic reticulum stress and initiate cell death through the activation of several pathways and, consequently, graft rejection. In addition, whereas less than 5% of non-steatotic grafts are associated with a primary non-function rate, steatotic livers present a ratio of 60%. This is especially relevant if the donor age is greater than 70 years. Furthermore, steatotic livers show several disturbs that worsen the effect of IRI, including a lower number of sinusoids, mitochondrial dysfunction, and microvascular alterations. In addition, hepatocytes are more susceptible to lipid breakdown due to the presence of excessive fat and/or greater production of reactive oxygen species (ROS). This process is known as lipid peroxidation (LP).

Melatonin, produced by the pineal gland as well as by several other organs, is a well-known powerful antioxidant. Its antioxidant activity is produced due to both direct and indirect actions. The first one is based on its capacity as a free radical scavenger, whereas the last one is generated via the increase the cellular antioxidant defense system by rising mRNA levels as well as the activities of several antioxidant enzymes. In addition, several studies observed melatonin's role during IRI and its capacity against LP disturbs. Due to that, the indoleamine has been suggested to may play an important role preventing graft rejection.

In this mini-review we summarize the protective effect of melatonin against molecular hepatic damage produced during organ transplantation due to on ischemia-reperfusion injury. We are going to focus especially in liver steatotic transplantation.

Keywords: *Liver; Ischemia-Reperfusion; Melatonin; Transplantation; Liver Steatosis*

Abbreviations

PP: Periportal Area; CL: Centrilobular Regions; KC: Kupffer Cells; HSC: Hepatic Stellate Cells; SEC: Sinusoidal Endothelial Cells; G6P: Glucose-6-Phosphatase; IRI: Ischemia-Reperfusion Injury; ER: Endoplasmic Reticulum; ROS: Reactive Oxygen Species; RNS: Reactive Nitrogen Species; ATP: Adenosine Triphosphate; IL: Interleukins; TNF-α: Tumor Necrosis Factor-Alpha; O2·-: Superoxide Radical; H_2O_2: Hydrogen Peroxide; ·OH: Hydroxyl Radical; LP: Lipid Peroxidation; MDA: Malondialdehyde; 4-HNE: 4-Hydroxynonenal; NO·: Nitric Oxide;

eNOS: Endothelial Nitric Oxide Synthase; nNOS: Neuronal Nitric Oxide Synthase; iNOS: Inducible Nitric Oxide Synthase; ONOO-: Peroxynitrite Anion; GPx: Glutathione Peroxidase; GRd: Glutathione Reductase; GSH: Glutathione; MDDP: Multidrug Preconditioning Procedure.

Introduction

Several vital functions are regulated by liver, including the efficient uptake, storage and metabolism of carbohydrates, amino acids, cholesterol, bile acids, lipids, proteins and vitamins for storage and metabolism [1]. Hepatic blood flow is 1,500 mL per minute (25% of cardiac output). The two main vascular supplies to the liver are the portal vein and the hepatic artery. The first provides about 70% of the blood flow whereas the second supplies 30% of the flow [2]. It is known that the periportal area (PP) and the centrilobular regions (CL) of this tissue have different roles in liver function owing to gradient differences in cell and matrix composition. These differences attending to their functional properties explain the distribution of lesions as well as the susceptibility of cells to hepatotoxicants. Liver cells, including hepatic stellate cells (HSC), Kupffer cells (KC), and sinusoidal endothelial cells (SEC) also have gradients [2,3]. Secondary to this situation, PP hepatocytes usually show increased levels of oxygen saturation, glucose-6-phosphatase (G6P) activity, peroxisomes, bile acid uptake, urea cycle activity, glutathione content, and glycogen synthesis. On the other hand, detoxification is a principal function of CL regions with the exclusive expression of glutamine synthetase and higher levels of other enzymes such as glucokinase and carboxylesterase compared to PP [1,2].

In both acute and chronic liver diseases, transplantation is the last-resort treatment. However, this treatment may fail due to an inherent process in organ transplantation, the ischemia-reperfusion injury (IRI). In fact, IRI is involved in 81% of re-transplantations during the first week after surgery due to primary non-function or poor function of liver allograft [3,4]. These results are produced due to prolonged cold storage, especially if steatosis disease is preset. During cold IRI, steatotic livers exacerbate endoplasmic reticulum (ER) stress and initiate cell death through the activation of several pathways and, consequently, graft rejection [5-8].

Melatonin (N-acetyl-5-methoxytryptamine), produced by the pineal gland as well as by many other organs including placenta, testes, bone marrow, ovary, gut, and liver, is a well-known powerful antioxidant [9-13]. It is tryptophan derivate produced in a process regulated by the action of four enzymes: tryptophan hydroxylase, L-aromatic amino acid decarboxylase, N-acetyltransferase and acetylserotonin methyltransferase [14]. Melatonin is both a biological rhythm regulator and an important component of the antioxidant defense system [12,13,15,16].

Herein, we summarize the protective effect of melatonin against molecular hepatic damage produced during organ transplantation due to on ischemia-reperfusion injury. In this mini-review we are going to focus especially in liver steatotic transplantation.

Ischemia-reperfusion injury

IRI is a pathological condition characterized by an initial hypoxia (caused by the restriction of blood supply) followed by reoxygenation (due to the flow restoration). The latter process produces an exacerbation of tissue damage and an increased inflammatory response [17].

During IRI, several nonimmunological antigen-independent events are produced in the liver. This includes microcirculatory dysfunction that causes failure of vascular perfusion and damage to the liver SEC, release of proinflammatory mediators that infiltrate the tissue with leucocytes, and cellular necrosis and apoptosis [18,19]. IRI also includes oxidative stress secondary to the imbalance between increased free radical production and decreased antioxidant defense [20,21].

Activation of polymorphonuclear leucocytes, endothelial cells, reactive oxygen species (ROS) and reactive nitrogen species (RNS) are known to be critical in the pathogenesis of IRI [22-24]. Cold ischemia causes parenchymal cell death as a result of several cellular metabolic disturbances, including glycogen consumption, decreased oxygen supply, adenosine triphosphate (ATP) depletion, degradation of ATP into its metabolites (adenosine, inosine and hypoxanthine) and generation of xanthine dehydrogenase from xanthine oxidase. Conversely, reperfusion injury implies an inflammatory immune response with the release of inflammatory mediators, including interleukins (IL) and tumor necrosis factor-alpha (TNF-α). Both of them cause oxidative stress injury as well as recruitment of leucocytes [25,26].

During reperfusion, increased ROS levels are generated due to the ATP metabolites production. ROS include superoxide radical (O_2·-), hydrogen peroxide (H_2O_2), and hydroxyl radical (·OH) [27,28]. ·OH activity leads to destruction of polyunsaturated fatty acids, proteins and nucleic acids. The chain reaction that destroys lipids is referred to as lipid peroxidation (LP) and contributes to cell edema due to a disruption of normal fluidity and permeability of cell membranes, massive overload of Ca^{2+} and N^{a+}, discharge of cytochrome c into the cytoplasm from the mitochondria with the subsequent activation of caspase activities and cell lysis [29-31]. Malondialdehyde (MDA) as well as 4-hydroxynonenal (4-HNE) are produced during LP and are used as markers of ROS-dependent tissue damage. MDA produces fibrosis via activation of HSC, which stimulate collagen production. Also, it contributes to inflammation by activating NF-kB, which regulates the expression of proinflammatory cytokines. 4-HNE has a chemoattractant activity on neutrophils [32].

RNS also plays an important role in IRI. Nitric oxid (NO·) is produced by endothelial (eNOS), neuronal (nNOS) and inducible (iNOS) nitric oxide synthase (NOS) (eNOS, nNOS, and iNOS, respectively) [33,34]. The first one is expressed exclusively in SEC and releases small amounts of NO·. In contrast, iNOS synthesizes large amounts of NO· and is transcriptionally up-regulated in all liver cells in response to inflammatory mediators. In addition, eNOS is purposed as an important protective agent against vascular endothelial pathophysiology whereas iNOS is suggested to raise ischemic injury due to the increased free radical formation. This is indicated since eNOS-derived NO· is produced early and may prevent the microcirculatory disturbs of engraftment and reperfusion. Conversely, iNOS-derived NO· is generated several hours after and its production is harmful at this time [35,36].

During IRI, NO· levels are decreased as a consequence of both reduced production and increased ROS scavenging activity. ROS, increased in IRI, modulate the intensity of this process by regulating platelet aggregation and neutrophil adhesion [37]. In addition, IRI implies an endothelial dysfunction, including a reduction in eNOS function due to the activity of the endogenous competitive inhibitors, the increased levels of peroxynitrite anion (ONOO-) (an extremely non-radical reactant secondary to the couple of NO· with O_2·-) and cell-free hemoglobin, and the oxidation of guanylyl cyclase due to the activity of NO· [38].

The antioxidant capacity of melatonin is based on its direct action as a free radical scavenger as well as indirect antioxidative actions via its ability to stimulate the cellular antioxidant defense system by increasing mRNA levels and the activities of several important antioxidant enzymes [39,40]; these include superoxide dismutase (SOD, which catalyze the conversion of O_2·- to H_2O_2), glutathione peroxidase (GPx) and glutathione reductase (GRd) and glutamylcysteine ligase which promote the synthesis of another important intracellular antioxidant, glutathione (GSH) [41-43]. Melatonin has potent scavenging activities on ROS, RNS [44]. Additionally, melatonin limits ONOO- generation by curtailing the activity of iNOS [45]. Melatonin also has been shown to preserve the functional and energetic states during IRI by reducing concentrations of TNF-α and NO· due to a rise in eNOS mRNA levels, whereas it lowers the elevation of iNOS mRNA levels inhibiting iNOS expression [46]. Several studies observed that melatonin protects against the IRI-induced impairment of mitochondrial respiration, mitochondrial swelling, ATP synthesis, and LP [47-50].

Liver transplantation: steatotic grafts

In both acute and chronic liver diseases, transplantation is the last-resort treatment. However, this treatment may fail due to an inherent process in organ transplantation, the IRI. In fact, IRI is involved in 81% of re-transplantations during the first week after surgery due to primary non-function or poor function of liver allograft [51,52]. These results are produced due to prolonged cold storage, especially if steatosis disease is preset. During cold IRI, steatotic livers exacerbate ER stress and initiate cell death through the activation of several pathways and, consequently, graft rejection [53-55]. Due to the activity of melatonin against IRI and oxidative stress, the role of the indoleamine again graft rejection in steatotic livers has been studied (Table 1).

Steatotic liver grafts

60% of steatotic liver grafts are associated with a primary non-function rate compared with less than 5% for non-steatotic grafts [6,59]. This is especially relevant if the donor age is greater than 70 years. Furthermore, these donors often show an increased incidence of liver steatosis [60]. On the other hand, non-heart-beating donor organs suffer a prolonged warm ischemia before cold preservation and are also associated with a very high risk of primary non-function [61].

Authors	Methods	Results
Zaouali., *et al*. [56]	Combined effect of melatonin and trimetazidine as additives to IGL-1 solution in the modulation of ER stress and autophagy in steatotic liver grafts through activation of AMPK. IGL-1 was enriched with trimetazidine (10^{-3} µM) + melatonin (100 µM). Hepatic injury (ALT and AST) function (bile production) and endoplasmic reticulum (ER) stress (GRP78, PERK, and CHOP) and autophagy (beclin-1, ATG7, LC3B, and P62) were measured.	Melatonin ant trimetazidine generate lower injury and better function. In addition, a significant decrease in GRP78, pPERK, and CHOP activation after reperfusion were also observed. This was consistent with a major activation of autophagic parameters (beclin-1, ATG7, and LC3B) and AMPK phosphorylation. The inhibition of AMPK induced an increase in ER stress and a significant reduction in autophagy.
Kireev., *et al*. [48]	Forty Zucker rats subjected to 35 min of warm hepatic ischemia and 36h of reperfusion. Melatonin (10mg/kg) was administrated intraperitoneally or orally. Plasma ALT, AST and hepatic content of ATP, MDA, hydroxyalkenals, NO metabolites, antioxidant enzyme activity, caspase-9 and DNA fragmentation were determined in the liver. iNOS, eNOS, Bcl2, Bax, Bad and AIF expressions were determined by RT-PCR.	Melatonin was effective decreasing liver injury due to its capacity to maintain liver transaminases, markers of apoptosis, of oxidative stress and improving ATP content. It was produced due to the capacity of the indoleamine recovering mitochondrial dysfunction and improving the ability of the steatotic hepatocyte to produce ATP. Melatonin was able to decrease gene expression of pro-apoptotic genes, and also prevented caspase-9 activation, which initiates the intrinsic or mitochondrial pathway of apoptosis.
von Heesen., *et al*. [57]	A multidrug donor preconditioning (MDDP) process before 24 h of cold ischemia was performed. MDDP include pentoxyphylline (50 mg/kg), glycine (100 mg/kg), deferoxamine (30 mg/kg), N-acetylcysteine (150 mg/kg), erythropoietin (1000 IU), melatonin (10 mg/kg), and simvastatin (5 mg/kg). MDDP was applied before liver perfusion with 4°C histidine-tryptophan-ketoglutarate (HTK) solution and organ harvest. After 60 min of reperfusion, bile volume, ALT, AST, LDH, MDA, IL-1, GDH and histopathological disturbs were measured.	MDDP showed a significant reduction of bile flow as well as a marked increase of liver enzyme levels and apoptotic cell death. This was associated with an increased MDA formation, IL-1 production, and leukocytic tissue infiltration.
Zaouali., *et al*. [58]	Melatonin was added to Institute Georges Lopez (IGL-1) solution during 24 h (4°C). Thereafter, livers were subjected to 2-hr reperfusion (37°C). Transaminases, bile production and sulfobromophthalein (BSP) clearance, (marker of vascular resistance), oxidative stress and related inflammatory mediators including nitric oxide and cytokines were measured.. Cytoprotective factors as hemeoxygenase 1 (HO-1) were also studied.	Lower transaminase levels and higher bile production and BSP clearance were observed in fatty livers preserved in IGL-1 solution enriched with melatonin. The melatonin benefits correlated with the generation of nitric oxide (through constitutive e-NOS activation) and the prevention of oxidative stress and inflammatory cytokine release including tumor necrosis factor and adiponectin, respectively.

Steatotic livers show several disturbs that worsen the effect of IRI, including a lower number of sinusoids, mitochondrial dysfunction, and microvascular alterations [62]. Furthermore, hepatocytes are more susceptible to lipid breakdown due to the presence of excessive fat and/or greater production of ROS [63]. In obese rat model, elevated peroxisomal fatty acyl-CoA oxidase, which constitutes an important source of increased H_2O_2, was reported [64]. As summarized above, melatonin is highly protective against IRI under all of these circumstances.

It is documented that bilirubin (a breakdown product of hemoglobin) and other bile pigments may play an important role in the circulation as a critical endogenous vasoprotector system due to its antioxidant and anti-nitrosative capacities [65,66]. In rat models, the addition of melatonin to the perfusion medium increased bile production in a dose-dependent manner and improved bile bilirubin excretion and tissue ATP levels during IRI [67]. Another study documented a relationship between the bile flow rates and cellular ATP levels and it was demonstrated that ATP levels also correlate with the bile acid output. The excretion of bile acids may provide a useful parameter for evaluating the hepatic energy status, which is essential for organ viability [68]. Furthermore, melatonin (500 µg/kg/day/i.p.) may induce a hepatoptotective effect against the liver injury secondary to acute ligation of the biliary duct; as such, melatonin lowers the negative parameters of cholestasis [69].

In a rat liver model [70], a multidrug preconditioning procedure (MDDP) based on curcumin, simvastatin, N-acetylcysteine, erythropoietin, pentoxyphylline, melatonin, glycine, and methylprednisolone was used to reduce hepatic damage. During cold ischemia for 24 h with organ storage in HTK and reperfusion of 60 minutes, the authors concluded that melatonin's preventive actions on reperfusion injury may have been responsible for the benefits of the MDDP procedure by abrogating the oxygen radical actions and thus the MDA accumulation. They noted that MDDP almost completely prevents manifestation of post-ischemic reperfusion injury.

Another MDDP based on pentoxyphylline, glycine, deferoxamine, N-acetylcysteine, erythropoietin, melatonin, and simvastatin for donor precondition was studied by von Heesen., *et al.* [57] in a rat steatotic liver model with the same process used by Moussavian., et al [70]. They found a significant reduction in post-ischemic dysfunction and reperfusion injury not only in steatotic donors but also in normal rat livers versus that in control tissues. Furthermore, MDDP was effective in reducing the leucocytic infiltrative response (increased in steatotic livers compared with non-steatotic controls) and reduced ROS injury. However, it was not possible to identify the specific beneficial actions of melatonin in this study.

A study [71] reported ATP levels in livers preserved with either University of Wisconsin or Celsior solutions and reperfused without melatonin had ATP levels about 7 times lower than the control livers. When melatonin was used during reperfusion (100 μM administered i.v.), significant increases in hepatic ATP and of bile production were observed with both solutions. Melatonin-treated rats showed similar levels of both LDH and GSH levels compared to control animals. ROS-mediated edema and ROS levels were less intense after melatonin was incorporated into the preservation solution.

The combined effect of melatonin and trimetazidine (TMZ at 10-3 μM + MEL 100 μM) as additives to IGL-1 solution in the modulation of ER stress and autophagy in steatotic liver grafts were also evaluated by Zaouali., *et al* [56]. This study was concerned with the activation of AMPK, an enzyme that increases activity during IRI which leads to the inhibition of lipogenesis, protein synthesis and glucose generation, and enhanced fatty acid oxidation [72]. It has been observed that there is a relationship between AMPK activation and accumulation of α subunit of hypoxia-inducible factor-1 (HIF-1α, a transcription factor, which functions as a master regulator of adaptive responses to reduced O_2 availability) [73]. Furthermore, AMPK activation induces NO· generation via eNOS activation during IRI [176] and this process in the fatty liver impairs normoxic degradation of HIF-1α and contributes to its stabilization [74]. This group demonstrated that AMPK activation induced by TMZ+MEL enhanced eNOS induction and, consequently, HIF-1α stabilization. TMZ+MEL caused the stimulation of protective genes including heat shock protein 70 (HSP70), erythropoietin, bcl-2, vascular endothelial growth factor (VEGF) and HO-1 [71,75]. In addition, IGL-1 preservation solution added to the TMZ+MEL cocktail also decreased ER stress and increased autophagy in fatty liver grafts due to the modulated AMPK activity [75,76].

Conclusion

In both acute and chronic liver diseases, transplantation is the last-resort treatment. IRI, inherent in liver transplantation, is responsible of several re-transplantations, being more frequently observed in steatotic liver grafts. Melatonin, a well-recognized antioxidant due to its capacity to stimulate the innate immune response, promote the activity of several antioxidant enzymes, as well as its role as a free radical scavenger, may play a protective effect in liver transplantation. These effects are suggested to be produced in both steatotic and non-steatotic grafts. More studies are required to confirm these theories, especially in humans.

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