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TOPIC HIGHLIGHT

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Hepatoprotective actions of melatonin: Possible mediation by melatonin receptors

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Abstract

Melatonin, the hormone of darkness and messenger of the photoperiod, is also well known to exhibit strong direct and indirect antioxidant properties. Melatonin has previously been demonstrated to be a powerful organ protective substance in numerous models of injury; these beneficial effects have been attributed to the hormone's intense radical scavenging capacity. The present report reviews the hepatoprotective potential of the pineal hormone in various models of oxidative stress *in vivo*, and summarizes the extensive literature showing that melatonin may be a suitable experimental substance to reduce liver damage after sepsis, hemorrhagic shock, ischemia/reperfusion, and in numerous models of toxic liver injury. Melatonin's influence on hepatic antioxidant enzymes and other potentially relevant pathways, such as nitric oxide signaling, hepatic cytokine and heat shock protein expression, are evaluated. Based on recent literature demonstrating the functional relevance of melatonin receptor activation for hepatic organ protection, this article finally suggests that melatonin receptors could mediate the hepatoprotective actions of melatonin therapy.

INTRODUCTION

It has been suggested that the substance melatonin (5-methoxy-N-acetyltryptamine), discovered by Aaron Lerner in 1958, exists in almost every animal species, and possibly even in all plants[1,2]. Its physiological functions are said to be diverse; while melatonin may be involved in modifications of vasomotor tone[3,4] and thermoregulation[5], it is primarily known as the signal of darkness[6].

In vertebrates, melatonin is synthesized in the pineal gland and secreted during darkness as a hormonal message of the photoperiod[7]. The rhythm of melatonin synthesis is mainly driven by an oscillator which is situated in the hypothalamic suprachiasmatic nucleus (SCN)[8]. This oscillator is usually entrained to a 24-h rhythm by environmental lighting conditions, which are perceived in the retina by rods, cones and intrinsically photosensitive retinal ganglion cells[9].

Based on the photoperiodic information transduced from the retina *via* the SCN to the pineal gland, melatonin is secreted during darkness after *de-novo* synthesis from tryptophan[10]. This nocturnal melatonin signal is proportional to the length of the night, thus encoding not only

circadian, but also seasonal variations in the photoperiod[11]. In so-called photoperiodic animals, like the Siberian hamster, these seasonal variations in melatonin output may have a profound influence on the regulation of reproduction[12,13], prolactin secretion[14], as well as coat color[15]. The nocturnal secretion of melatonin is generally independent of an animal's active period: in both nocturnal and diurnal species, melatonin levels rise during darkness[6].

Melatonin synthesis is not exclusively located in the pineal gland, but has also been described in numerous peripheral organs, such as the retina[16], bone marrow[17], skin[18], Harderian gland[19], platelets[20], lymphocytes[21], testes[22], and in the gastrointestinal tract[23]. Data on messenger RNA expression of two key enzymes responsible for melatonin synthesis, arylalkyamine-N-acetyltransferase and hydoxyindole-O-methyltransferase, suggest that even more peripheral organs may be able to produce this hormone[24].

So far, the physiological significance of extrapineal sites of melatonin synthesis remains unclear. However, besides its relevance in the time-keeping system, melatonin has been demonstrated to be a powerful radical scavenger[25]; it is tempting to assume that extrapineal melatonin may serve as a tissue protective agent.

MELATONIN AS AN ANTIOXIDANT

Processes of acute inflammation, e.g. sepsis, hemorrhagic shock or ischemia/reperfusion, typically result in an imbalance of oxidative homeostasis with excess generation of reactive oxygen species (ROS) and a relative deficiency of endogenous antioxidants; this state is called oxidative stress. ROS include oxidants, such as peroxynitrite, and free radicals, such as hydroxyl radicals and superoxide; these substances are toxic and may induce lipid peroxidation (LPO), as well as protein, sugar and DNA degradation[26].

The powerful antioxidant capacity of melatonin is usually attributed to its potential to eliminate free radicals by the donation of electrons[27,28]. For example, melatonin may neutralize hydroxyl radicals by forming 3-hydroxymelatonin, which is excreted in the urine[29]. Furthermore, melatonin was demonstrated to interact with toxic reactants like peroxyl radicals[30], singlet oxygen species[31], and hydrogen peroxide[32]. Metabolites of melatonin, including the major hepatic metabolite 6-hydroxymelatonin, as well as N-acetyl-N-formyl-5-methoxykynuramine and N-acetyl-5-methoxykynuramine have been shown to detoxify radicals themselves[32-34]. This powerful pyramid scheme of radical scavenging has been named "the antioxidant cascade of melatonin"[1,34].

In addition to these direct interactions with ROS, melatonin may induce upregulation of the activity of antioxidants and antioxidant enzymes, such as superoxide dismutase (SOD), glutathione (GSH), glutathione peroxidase (GPx) and glutathione reductase (GSR), in the environment of oxidative stress[35,36]. In addition, the pineal hormone may induce downregulation of pro-oxidant enzymes like nitric oxide synthase (NOS)[37,38] and lipoxygenases[39], thus reducing the formation of nitric oxide (NO), superoxide anions, and subsequently peroxynitrite anions.

Both the direct detoxification of radicals, as well as the modification of pro- and antioxidative enzyme activities are thought to be relevant for the pineal hormone to act as a protective substance, for example when administered in models of oxidative stress. This valuable effect appears to be independent of the type of injury and the species investigated. Exogenous melatonin may exhibit beneficial actions in a myriad of models of organ damage; this is especially true for the liver.

HEPATOPROTECTION BY MELATONIN ADMINISTRATION

With respect to its hepatoprotective effects, countless publications have demonstrated that exogenous melatonin may be used successfully to treat a great variety of different pathophysiological conditions[40-146]: Table 1 gives an overview of the hepatoprotective effects of exogenous melatonin administration, without the pretension of being complete. Included in this summary are investigations mainly presenting a model of liver damage *in vivo*, evaluating parameters of hepatic integrity as a major endpoint, and the administration of melatonin as the primary therapeutic agent. Studies on chronic disease development, aging, investigations on nutritional or dietary changes, exercise-induced stress, remote organ injuries with the liver as a secondary target, as well as investigations on tumor development, cancer progression and liver metastases were excluded.

Based on this extraordinary pool of data, treatment with melatonin appears to be a versatile hepatoprotective strategy in models of experimental liver injury as demonstrated *in vivo* for rats, mice and chicks. There are remarkable variations concerning both the route of melatonin administration, as well as the dose given, the latter ranging a thousand-fold from 100 μg/kg[93,124] to 100 mg/kg[77] melatonin. Only limited data are available on dose-response relationships, and most studies did not include measurements of plasma melatonin levels. Furthermore, it should be mentioned that in some investigations, melatonin was given either as a single dose or repetitively - in some publications for weeks - as a pretreatment, before or while the damage was induced. Unfortunately, not all researchers used melatonin as a therapeutic substance following the infliction of damage, although this would be of high relevance for the evaluation of its clinical use.

Nevertheless, all these studies show similar or even identical results concerning the hepatoprotective effects of treatment with melatonin. Improvements are consistently demonstrated for - but not limited to - parameters of antioxidant enzymes, hepatocellular integrity, interleukin response, NO signaling, and survival.

Antioxidant effects

A strong antioxidant effect of melatonin seems evident as almost all investigators describe that in liver homogenates,

Table 1 Hepatoprotective effects of melatonin in different models of stress

Model	Induction/type	Melatonin treatment	Hepatoprotective effects of melatonin	Species	Ref.
Septic shock	CLP/LPS/LPS + BCG	0.25-60 mg/kg ip/iv/*po* 1-10 ×	hLPO↓, AST/ALT/GGT/ALP/BIL↓, hGSH/hGPx/hSOD/hCAT↑, hNEC↓, hPMN infiltration↓, hTNF-α/hIL-1/hNO↓, 72-h survival rate↑	Rats, mice	[40-49]
Hemorrhagic shock	90 min (MAP 35)/40%	10 mg/kg iv 1 dose	AST/ALT/LDH↓, liver function PDR-ICG↑, hepatic perfusion↑, hNEC↓	Rats	[50-52]
Ischemia/reperfusion	40-60 min ischemia/ischemia + resection	10-20 mg/kg ip/im 1-5 ×	hLPO↓, AST/ALT/LDH↓, hGSH↑, hNEC↓, hMPO↓, hPMN infiltration↓, hTNF-α/hCAS/hAPO/hiNOS↓, 7-d survival rate↑	Rats	[53-62]
Surgical trauma	70% hepatectomy	10 mg/kg per day ip for 7 d	hLPO↓, hGSH↑, histological alterations↓	Rats	[63]
Toxic liver injury	δ-Aminolevulinic acid	10 mg/kg per day ip 7-14 d	hLPO↓, hepatic DNA damage↓	Rats	[64,65]
	Acetaminophen	10-100 mg/kg ip/*po*/sc 1 ×	hLPO↓, AST/ALT↓, hGSH↑, hMPO↓, hNEC↓, 72-h survival rate↑	Mice	[66-68]
	Adriamycin	2-6 mg/kg ip/sc 1-7 ×	hLPO↓, hGSH/hGPx/hCAT↑, hHSP 40/60/70↓	Rats, mice	[69-71]
	Aflatoxins	5-40 mg/kg per day ig/ip for 3-8 wk	hLPO↓, hGSH/hGPx↑, hCAS/hNO↓, hHSP-70↓, hNEC↓	Rats, chicks	[72-76]
	Allyl alcohol	100 mg/kg ip 1 ×	hLPO↓, AST/ALT/LDH↓, hGSH↑, hNEC↓	Rats	[77]
	Arsenic	10 mg/kg ip for 5 d	hLPO↓, hGSH/hSOD/hCAT↑	Rats	[78]
	Cadmium	10-12 mg/kg per day ip/*po* for 3-15 d	hLPO↓, hGSH/hGPx↑, hNEC↓	Rats, mice	[79-82]
	Carbon tetrachloride	10-100 mg/kg ip/sc 1-30 ×	hLPO↓, AST/ALT/ALP/LDH/BIL↓, hGSH/hSOD/hCAT↑, hXO↓, hNO↓, hTNF-α/hIL-1b/hNF-κB↓, hNEC↓	Rats, mice	[77,83-92]
	Cyclophosphamide	100 μg/kg per day *po* for 15 d	hLPO↓, hGSH↑	Mice	[93]
	Cyclosporin A	715 μg/kg per day ip for 14 d	hLPO↓, AST/ALT/GGT↓, hNEC↓	Rats	[94-96]
	Diazepam	5 mg/kg per day sc for 30 d	hLPO↓, hSOD/hGSH↑	Rats	[97]
	Dimethylnitrosamine	50-100 mg/kg per day ip for 14 d	hLPO↓, AST/ALT/ALP/BIL↓, hSOD/hGSH/hGPx/hHO-1↑, hTNF-α/hIL-1b/hIL-6/hNF-κB↓	Rats	[98,99]
	Diquat	20 mg/kg ip 1 ×	ALT↓, hepatic content of F2-isoprostane↓, 24-h survival rate↑	Rats, mice	[100,101]
	Doxorubicin	10 mg/kg sc for 7 d	hLPO↓, GGT/LDH↓	Rats	[102]
	Endosulfan	10 mg/kg ip for 5 d	hLPO↓, AST/ALT/LDH↓, hGSH↑, hMPO↓, hTNF-α/IL-1b↓	Rats	[103]
	Iodine	1 mg/kg per day ip for 14 d	Hepatic content of Schiff's bases↓	Rats	[104]
	Kainic acid	4-10 mg/kg ip 1 ×	Hepatic DNA damage↓	Rats	[105]
	Lead	10-30 mg/kg per day ig for 7-30 d	hLPO↓, hGSH/hGPx/hSOD↑, hNEC↓	Rats	[106,107]
	Methanol	10 mg/kg ip 2 ×	hLPO↓, hGSH/hGPx/hSOD/hCAT↑, hMPO/hNO↓	Rats	[108]
	Methotrexate	10 mg/kg per day ip for 5 d	hLPO↓, hGSH↑, hNEC↓	Rats	[109]
	Mercury-(Ⅱ)	10 mg/kg ip 2 ×	hLPO↓, hGSH↑, hMPO↓	Rats	[110]
	α-Naphthyliso-thiocyanate	10-100 mg/kg ip/*po* 1-4 ×	hLPO↓, AST/ALT/LDH/GGT/ALP/BIL↓, hSOD/hCAT↑, hMPO↓	Rats	[111-114]
	Nodularin	5-15 mg/kg per day ip for 7 d	hGPx/hSOD/hCAT↑	Mice	[115]
	Ochratoxin A	5-20 mg/kg ig/*po* 1-28 ×	hLPO↓, GGT/ALP↓, hGSH/hGPx/hSOD/hCAT↑, hNEC↓	Rats	[116-120]
	Paraquat	1-10 mg/kg ip 5-6 ×	hLPO↓, hGSH↑, LD50 of paraquat↑	Rats	[121,122]
	Phosphine	10 mg/kg ip 1 ×	hLPO↓, hGSH↑	Rats	[123]
	Safrole	0.1-0.2 mg/kg sc 2 ×	Hepatic DNA damage↓	Rats	[124]
	Thioacetamide	3 mg/kg ip 3-5 ×	hLPO↓, AST/ALT/LDH/ammonia↓, hGSH/hCAT↑, hiNOS/hNEC↓	Rats	[125-127]
	Zymosan	5-50 mg/kg ip 1-7 ×	hLPO/hMPO↓	Rats	[128,129]
Cholestasis	Bile-duct ligation	0.5-100 mg/kg per day ip/*po* for 7-13 d	hLPO↓, AST/ALT/GGT/ALP/BIL↓, hGSH/hGPx/hSOD/hCAT↑, hMPO↓, hNO↓, hNEC↓, iron disturbances↓	Rats	[130-140]
Ionizing radiation	Full-body; 0.8-6.0 Gray	5-50 mg/kg ip 1-5 ×	hLPO↓, AST/ALT/GGT↓, hGSH/hSOD/hGPx↑, hMPO/hNO↓, hepatic DNA damage↓	Rats	[141-145]
Malaria	Schistosoma mansoni	10 mg/kg per day ip for 30 d	hLPO↓, AST/ALT↓, hGSH/hSOD↑, 56-d survival rate↑	Mice	[146]

↑: Upregulation/increase/improvement; ↓: Downregulation/decrease/deterioration; ALT: Alanine transaminase; ALP: Alkaline phosphatase; AST: Aspartate transaminase; BCG: Bacillus Calmette-Guérin; BIL: Bilirubin; CLP: Cecal-ligation and puncture; GGT: γ glutamyl transferase; hAPO: Hepatic apoptosis; hCAT: Hepatic catalase; hCAS: Hepatic caspase; hGPx: Hepatic glutathione peroxidase; hGSH: Hepatic glutathione; hHSP: Hepatic heat shock protein; hHO-1: Hepatic heme oxygenase 1; hIL: Hepatic interleukin; hiNOS: Hepatic inducible nitric oxide synthase; hLPO: Hepatic lipid peroxidation; hMPO: Hepatic myeloperoxidase; hNEC: Hepatocellular necrosis; hNF-κB: Nuclear factor κ-light-chain-enhancer of activated B cells; hNO: Hepatic nitric oxide; hPMN: Hepatic polymorphonuclear granulocytes; hSOD: Hepatic superoxide dismutase; hTNF-α: Hepatic tumor necrosis factor α; hXO: Hepatic xanthine oxidase; ig: Intragastrically; im: Intramuscularly; ip: Intraperitoneally; iv: Intravenously; LD: Lethal dose; LDH: Lactate dehydrogenase; LPS: Lipopolysaccharide; MAP: Mean arterial pressure; PDR-ICG: Plasma disappearance rate of indocyanine green; *po*: *Per os*; sc: Subcutaneously.

melatonin strongly attenuated hepatic LPO[40-49,53-99,102,103,106-114,116-123,125-146], usually measured by means of malondialdehyde quantification. Furthermore, melatonin appears to increase the activity and/or expression of hepatic antioxidant enzymes, such as GSH, GPx and SOD, after most types of injury[40-49,53-63,66-93,97-99,103,106-123,125-127,130-146]. Many in-

vestigators also report an increase in hepatic catalase after melatonin treatment[44,71,78,83-85,89,108,111,115,116,118,125,132,135,139].

Hepatocellular integrity

Administration of the pineal hormone appears to reduce the rise in serum enzyme levels of aspartate transaminase, alanine transaminase, lactate dehydrogenase, alkaline phosphatase, γ glutamyl transferase and bilirubin after almost all types of injury, indicating that the extent of cell damage was reduced[40-62,66-68,77,83-92,94-96,98-103,111-114,116-120,125-127,130-146]. This is supported by histopathology results when performed, showing that animals treated with melatonin typically presented with reduced hepatocellular necrosis or attenuated infiltration of polymorphonuclear granulocytes. Reduced hepatic levels of myeloperoxidase further indicate that neutrophil granulocyte infiltration was strongly reduced by the pineal hormone[41,55,67,108,109,111,134,143].

Interleukin response

With respect to interleukin signaling, melatonin was reported to suppress the formation of pro-inflammatory cytokines such as tumor necrosis factor α, interleukin (IL)-1, IL-1β, IL-6, as well as the cellular interleukin response protein, nuclear factor κ-light-chain-enhancer of activated B cells[42,43,53,62,88,99]. This was demonstrated in sepsis and after ischemia/reperfusion, as well as after carbon tetrachloride and dimethylnitrosamine toxicity. Thus, parts of the hepatoprotective actions of the pineal hormone could be based on its suppressive effects on the pro-inflammatory pathway of the immune response.

NO signaling

A large number of studies have investigated the relevance of the NO pathway in the protective effects of melatonin treatment[40,42,43,45,47,49,53,56,57,60,72,73,75,108,125,128,129,142,146]. Melatonin seems to reduce NO release in the vasculature and attenuate the expression of inducible NOS in the liver, as was demonstrated in models of sepsis, ischemia/reperfusion, cholestasis, ionizing radiation, and toxic liver injury with aflatoxins, carbon tetrachloride, methanol, and thioacetamide. As NO reacts with superoxide to form the potentially toxic oxidant peroxynitrite, the reduction in the expression of iNOS may well be another key element in the antioxidant potential of melatonin.

Survival

When investigated, the observed hepatoprotective effects of melatonin were associated with an improvement in survival rate or mean survival time, which was observed in models of sepsis, ischemia/reperfusion, acetaminophen and diquat toxicity, and malaria[41-43,49,53,60,68,101,146].

Taken together, the results from more than 100 experimental studies included here, show convincingly that various regimens of melatonin treatment may be used to reduce hepatic damage in acute liver injury *in vivo*[40-146]. However, this overview is likely to be incomplete: many other studies indicate similar results for chronic disease development and tumor therapy.

So far, only one investigation has been published regarding hepatoprotection by melatonin in humans: in a prospective study, increased survival, attenuated liver damage and reduced immunological activity after transcatheter arterial chemoembolization (TACE) and melatonin treatment were reported in patients with inoperable advanced hepatocellular carcinoma, compared with control patients who underwent TACE but were not given melatonin[147].

Limitations of melatonin

Despite the enormous amount of data supporting the idea of melatonin as a liver protective agent, it should be noted that there are reports which show no hepatoprotective effect of melatonin in a few models of stress. Daniels *et al*[148] were unable to demonstrate any benefit of melatonin administration with respect to carbon tetrachloride-induced liver injury *in vivo*, although ten other studies unanimously showed the value of such a treatment[83-92]. Furthermore, melatonin had no effect on 2-nitropropane-induced LPO in rat liver[149].

Equally interesting and disappointing, melatonin does not appear to be a protective agent with respect to hepatic ethanol toxicity. In a model of acute or chronic ethanol exposure, melatonin administration did not influence hepatic LPO, or GSH and GPx activities in rat[150]. El-Sokkary *et al*[151] demonstrated that administration of ethanol for 30 d did not increase hepatic LPO in the same species. Yet, a recent study showed that melatonin may reduce ethanol-induced liver injury in terms of reduced hepatocellular injury and inflammatory response in a rodent model[152]. As a consequence, further data are required to resolve the issue on whether melatonin may be helpful in reducing ethanol-associated liver damage.

Both positive and negative findings raise the question of how melatonin's intense hepatoprotective potential may be mediated. With respect to this matter, it has been suggested that the activation of membrane-bound melatonin receptors may be an important step in the induction of the antioxidant properties of the pineal hormone[35,36].

HEPATIC MELATONIN RECEPTORS

Melatonin receptors in mammals are classified as membrane-bound, high-affinity G-protein coupled receptors, officially named MT_1 and MT_2 (previous terminology: Mel_{1a} and Mel_{1b}, respectively)[153]. Both receptors are coupled to heterotrimeric G-proteins, and involve signaling through inhibition of cyclic adenosine-monophosphate (cAMP) formation, protein kinase A activity and phosphorylation of cAMP responsive element binding, as well as effects on adenyl cyclases, phospholipase A2 and C, and calcium and potassium channels[154-158]. A third receptor, named MT_3, was demonstrated to be equivalent to intracellular quinone-reductase-2[159]. Non-mammalian species express yet another receptor subtype named Mel_{1c}, which is the first type of melatonin receptor to be discovered[160].

In the liver, the presence of MT_1, MT_2 and MT_3 has been reported in various species[161-171]; Table 2 gives an

Table 2 Melatonin receptors in the liver of various species

Species	MT1	MT2	MT3/QR2	Technique	Ref.
Wistar rat	+	+	NT	RT-PCR	[161,162]
CH3/He mouse	+	+	NT	RT-PCR	[163]
Swiss mouse	+	-	NT	RT-PCR	[164]
Sprague-Dawley rat	-	+	NT	RT-PCR	[165]
Golden rabbitfish	+	+	NT	RT-PCR	[166,167]
European sea bass	-	+	NT	RT-PCR	[168]
Senegalese sole	+	-	NT	RT-PCR	[169]
Syrian hamster	NT	NT	+	Iodine ligand	[170,171]
CD-1 mouse	NT	NT	+	Iodine ligand	[170]
Dog	NT	NT	+	Iodine ligand	[170]
Cynomolgus monkey	NT	NT	+	Iodine ligand	[170]

+: Detected; -: Not detected; MT1: Melatonin receptor type 1; MT2: Melatonin receptor type 2; MT3/QR2: Melatonin receptor type 3/quinone reductase-2; NT: Not tested; RT-PCR: Reverse transcription-polymerase chain reaction.

overview on the current literature demonstrating hepatic melatonin receptor expression or specific iodine ligand binding. So far, there are no original research publications showing proof of hepatic MT_1 or MT_2 receptors in humans. Some evidence points to the possibility that melatonin receptor expression may exhibit circadian variations; this has also been demonstrated for hepatic MT_1 and MT_2[163,166-168].

The physiological significance of hepatic melatonin receptors is mostly unknown. Two studies indicated that hepatic melatonin receptors may be involved in regulating blood glucose[164,172]. Melatonin receptor double knock-out mice do exist, and they appear to have a generally unaltered phenotype. So far, there are no reports showing disadvantages regarding the lack of hepatic melatonin receptors under physiological conditions.

Unfortunately, there are currently no reliable antibodies available for MT_1 and MT_2 receptors[154]. Only a few publications have demonstrated data on the MT_1 or MT_2 protein[162,173]; the results are either non-specific or cannot easily be reproduced. Thus, additional techniques will be required to convincingly demonstrate melatonin receptor protein in the liver.

Nonetheless, our own laboratory was able to generate preliminary results concerning the immunohistochemical distribution of MT_1 in the liver[173]. It appeared that MT_1 was primarily localized in the pericentral area of liver lobules. Due to their metabolic state, pericentral fields of the liver are particularly sensitive to ischemic stress, compared to slightly better oxygenated periportal areas. Thus, this differential distribution of melatonin receptors could provide a way of focusing melatonin receptor-dependent liver protection to areas in need. It is tempting to speculate that this pattern of MT_1 expression might allow the preferential protection of centrolobular hepatocytes.

Further studies, using different techniques or improved antibodies, will be required to support this idea of differentially distributed hepatic melatonin receptors. Thus, the presence and distribution of both melatonin receptor protein subtypes in the liver remain to be determined.

RECEPTOR-MEDIATED ACTIONS OF MELATONIN IN THE LIVER

Only a few studies have analyzed the significance of melatonin receptors in the hepatoprotective effects of melatonin administration *in vivo*[50,51,174]. In a model of hemorrhage and resuscitation, the melatonin receptor antagonist luzindole was able to attenuate the protective effects of melatonin pretreatment and therapy with respect to liver function as measured by plasma disappearance rate of indocyanine green[50,51]. However, not all of the beneficial effects of melatonin were abolished. The use of this antagonist may not clarify all aspects of the effects of melatonin administration, as luzindole itself has been demonstrated to have a strong direct antioxidant potential[175], and to reduce LPO *in vitro*[176].

In the same model of hemorrhagic shock, therapy with the selective melatonin receptor agonist ramelteon improved liver function and hepatic perfusion in rats[174]; this melatonin receptor agonist does not possess any relevant radical scavenging properties[174]. These results point to the possibility that although beneficial, the radical scavenging capacity of melatonin may not be necessary for its protective actions.

This hypothesis is supported by the observation that in other organ systems, the protective potential of melatonin may also be antagonized by luzindole: this antagonist has been reported to abolish the protective capacity of melatonin after myocardial ischemia/reperfusion injury[177], after cyclosporine-A cardiotoxicity[178], in a model of neonatal brain injury[179], and with respect to stress-induced gastric lesions[180].

The following preliminary data from our own research laboratory may have even more impact: in a murine model of sepsis, we were able to demonstrate that the improvements in survival seen after melatonin therapy were not present in melatonin receptor double knock-out mice. This finding indicates once more that membrane-bound melatonin receptors may be responsible for the beneficial effects of melatonin administration.

As a consequence, if (1) no radical scavenging properties are necessary to provide organ protection *via* melatonin receptor activation[174]; (2) the melatonin receptor antagonist luzindole may abolish almost all protective effects of melatonin[177-180]; and (3) the absence of melatonin receptors impedes the protective action of melatonin administration, then it appears reasonable to conclude that melatonin receptors are necessary to mediate at least some of the beneficial effects of the pineal hormone in peripheral organs.

POTENTIAL INFLUENCE ON HEPATIC GENE EXPRESSION

The specific intracellular signal transduction cascade leading to hepatoprotective effects after melatonin receptor activation is presently unknown. However, a number of

hypotheses have been published, suggesting that cAMP responsive element- or estrogen responsive element-containing genes may be regulated by melatonin receptor activation[35,181]. Most certainly, melatonin has a profound influence on hepatocellular gene expression; this has been demonstrated in heat shock protein expression by various investigators[69,73,95]. Our research group was able to present preliminary data showing that melatonin influences different pathways of hepatocellular transcription, including modifications of a variety of heat shock proteins, as well as intense regulation of other membrane-bound receptors and signal transduction factors, in a rat model of hemorrhagic shock[182]. These findings allow the assumption that melatonin therapy may induce beneficial changes with respect to gene transcription in hepatocytes, in the environment of oxidative stress. However, it remains to be determined whether these modifications of hepatic gene expression are indeed mediated by melatonin receptor activation.

FROM BENCH TO BEDSIDE

While the current literature leaves little doubt that melatonin administration may induce hepatoprotective actions[40-146], many questions remain on how this effect may be transduced. The putative signaling cascade, leading from melatonin receptor activation to specific hepatoprotective gene expression profiles, remains to be determined. Based on the evidence available, it appears possible that melatonin receptors mediate the intense protective effects of the pineal hormone in the liver.

To bring this experimental knowledge into clinical use, a pilot study was initiated by Schemmer *et al*[183] in Germany to evaluate the use of melatonin in patients undergoing major liver resections. Should this investigation be successful, this would open the door for yet another important indication for the use of melatonin in human liver surgery: as an adjunct to reduce ischemia/reperfusion injury in liver transplantation. The research group of Freitas and Vairetti has already demonstrated in two studies that melatonin may reduce cold ischemic injury in rat liver[184,185], and suggested that the pineal hormone may be useful in the event of liver transplantation. This idea was supported by Casillas-Ramírez in a review on liver transplantation[186]. Thus, melatonin administration could be beneficial in patients not only to reduce damage to the transplant, but also to serve as a protective agent for the attenuation of reperfusion injury.

Future studies will demonstrate whether melatonin will meet our high expectations not only in the laboratory, but also for our patients. However, the currently available literature allows us to believe that melatonin will successfully continue its way from bench to bedside as a powerful hepatoprotective agent.

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