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 plants1.2. Its physiological functions are said to be diverse; while melatonin may be involved in modifications of vasomotor tone3.4 and thermoregulation5, it is primarily known as the signal of darkness6.

In vertebrates, melatonin is synthesized in the pineal gland and secreted during darkness as a hormonal message of the photoperiod7. 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 cells9.

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 tryptophan10. This nocturnal melatonin signal is proportional to the length of the night, thus encoding not only
circadian, but also seasonal variations in the photoperiod\[1]\[2\]. In so-called photoperiodic animals, like the Siberian hamster, these seasonal variations in melatonin output may have a profound influence on the regulation of reproductive, prolactin secretion\[3\], as well as coat color\[4\]. 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\[5\].

Melatonin synthesis is not exclusively located in the pineal gland, but has also been described in numerous peripheral organs, such as the retina\[6\], bone marrow\[7\], skin\[8\], Harderian gland\[9\], platelets\[10\], lymphocytes\[11\], testes\[12\], and in the gastrointestinal tract\[13\]. Data on messenger RNA expression of two key enzymes responsible for melatonin synthesis, arylalkylamine-N-acetyltransferase and hydroxindole-O-methyltransferase, suggest that even more peripheral organs may be able to produce this hormone\[14\].

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\[15\], 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\[16\].

The powerful antioxidant capacity of melatonin is usually attributed to its potential to eliminate free radicals by the donation of electrons\[17,18\]. For example, melatonin may neutralize hydroxyl radicals by forming 3-hydroxyindole-2-carboxylic acid and 3-hydroxyindole-2,3-dicarboxylic acid, as well as the major hepatic metabolite 6-hydroxymelatonin, as well as hydrogen peroxide\[19\]. 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\[20\]. This powerful pyramid scheme of radical scavenging has been named “the antioxidant cascade of melatonin”\[21,22\].

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\[23,24\]. In addition, the pineal hormone may induce downregulation of pro-oxidant enzymes like nitric oxide synthase (NOS)\[25,26\] and lipoxygenases\[27\], 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\[28,29\]. 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 in 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 thousandfold from 100 µg/kg\[30\] to 100 mg/kg\[31\] 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,
Melatonin strongly attenuated hepatic LPO\(^{[40-49,53,99,102,103]}\), 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.

\[\begin{align*}
&\text{Table 1 Hepatoprotective effects of melatonin in different models of stress} \\
&\text{Model} \quad \text{Induction/type} \quad \text{Melatonin treatment} \quad \text{Hepatoprotective effects of melatonin} \quad \text{Species} \quad \text{Ref.}
\end{align*}\]

| Model                  | Induction/type | Melatonin treatment | Hepatoprotective effects of melatonin | Species | Ref. |
|------------------------|----------------|---------------------|---------------------------------------|---------|------|
| Septic shock           | CLP/LPS + BCG  | 0.25-60 mg/kg ip/i.p/3-10× | hLPO↓, AST/ALT/ALP/BIL↓, hGSH/hGPx/hSOD↓, hCAT↓, hNEC↑, MPMN infiltration↓, hTNF-α/hIL-1/hLNO↓, 72-h survival rate↑ | Rats, mice | \([40-49,53,99,102,103]\) |
| Hemorrhagic shock      | 90 min (MAP 35)%/40% | 10 mg/kg iv 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/hhNOS↓, 7-d survival rate↑ | Rats | \([53-62]\) |
| Surgical trauma        | 70% hepatopathy | 10 mg/kg per day ip for 7 d | hLPO↓, hGSH↓, histological alterations↓ | Rats | \([63]\) |
| Toxic liver injury     | s-Aminoolevulinic acid | 10-100 mg/kg ip/po/sc 1× | hLPO↓, hGSH↑, hepatic DNA damage↑ | Rats, mice | \([64-66]\) |
| Acetaminophen          | 10-100 mg/kg ip/po/sc 1× | hLPO↓, hGSH↑, histological alterations↓ | Mice | | |
| Adriamycin             | 2-6 mg/kg ip/sc 1-7× | 5-40 mg/kg per day ip/for 3-8 wk | hLPO↓, hGSH↑, hGPx/hCAT↑, hHSO↓, 40/60/70/ | Rats, mice | \([67-73]\) |
| Aflatoxins             | 100 mg/kg ip for d | hLPO↓, hGSH↑, hGPx/hCAT↑ | Rats | \([74\] |
| Arsenic                | 10 mg/kg ip for 5 d | hLPO↓, hGSH↑, hGPx/hCAT↑ | Mice | \([75-62]\) |
| Cadmium                | 10-12 mg/kg per day ip/po for 7-15 d | hLPO↓, hGSH↑, hGPx/hCAT↑ | Rats, mice | \([76-62]\) |
| Carbon tetrachloride   | 10-100 mg/kg ip/sc 1-30× | hLPO↓, AST/ALT/ALP/LDH/BIL↓, hGSH/hSOD/hCAT↑, hNO↓, hNO↓, hTNF-α/hIL-1/hLNO↓, hNEC↑ | Mice | \([77-83]\) |
| Cyclophosphamide       | 100 mg/kg per day po for 15 d | hLPO↓, hGSH↑ | Mice | | |
| Cyclosporin A          | 75-150 mg/kg per day for 14 d | hLPO↓, AST/ALT/LDH↓, hGSH↑, hMPO↑, hSOD/hCAT↑, hIL-1b/hIL-6/hIL-βx, hNEC↑ | Rats | \([84-86]\) |
| Diazepam               | 5 mg/kg per day sc for 30 d | hLPO↓, hGSH↑, hGPx/hCAT↑ | Rats, mice | \([87-89]\) |
| Dimethylnitrosamine    | 50-100 mg/kg ip per day for 10-15 d | hLPO↓, AST/ALT/ALP/BIL↓, hSOD/hGSH↑, hGPx↑, hNEC↑ | Rats | \([90-92]\) |
| Diquat                 | 20 mg/kg ip x | hLPO↓, hGSH↑, hGPx/hCAT↑, hNO↓, hNO↓, hTNF-α/hIL-1/hLNO↓, hNEC↑ | Mice | \([93-103]\) |
| Dexamethasone          | 10 mg/kg ip for 7 d | hLPO↓, hGSH↑, hGPx/hCAT↑, hMPO↓, hNO↓, hNO↓ | Rats | \([104-108]\) |
| Endosulfan             | 10 mg/kg ip for 5 d | hLPO↓, hGSH↑, hSOD/hCAT↑, hMPO↓, hNO↓ | Mice | \([109-110]\) |
| Iodine                 | 1 mg/kg per day for 4 d | hLPO↓, hGSH↑, hGPx/hCAT↑, hMPO↓, hNO↓ | Rats | \([111-114]\) |
| Kainic acid            | 4-10 mg/kg ip for 7× | hLPO↓, hGSH↑, hGPx/hCAT↑, hMPO↓, hNO↓ | Rats | \([115-116]\) |
| Lead                   | 10-30 mg/kg per day for 7× | hLPO↓, hGSH↑, hGPx/hCAT↑, hMPO↓, hNO↓ | Rats | | |
| Methanol               | 10 mg/kg ip for 5 d | hLPO↓, hGSH↑, hGPx/hCAT↑, hMPO↓, hNO↓ | Rats | | |
| Methotrexate           | 10 mg/kg ip for 5 d | hLPO↓, hGSH↑, hGPx/hCAT↑, hMPO↓, hNO↓ | Rats | | |
| Methylnitrosothioate   | 10-100 mg/kg ip/po 1-4× | hLPO↓, hGSH↑, hGPx/hCAT↑, hMPO↓, hNO↓ | Rats | | |
| Nodularin              | 5-15 mg/kg per day for 5 d | hLPO↓, hGSH↑, hGPx/hCAT↑, hMPO↓, hNO↓ | Rats | | |
| Ochratoxin A           | 5-20 mg/kg ip for 1-2× | hLPO↓, hGSH↑, hGPx/hCAT↑, hMPO↓, hNO↓ | Rats | | |
| Paraquat               | 5-10 mg/kg ip for 5× | hLPO↓, hGSH↑, hGPx/hCAT↑, hMPO↓, hNO↓ | Rats | | |
| Phosphine              | 10 mg/kg ip for 1× | hLPO↓, hGSH↑, hGPx/hCAT↑, hMPO↓, hNO↓ | Rats | | |
| Thioacetamide          | 3-8 mg/kg ip for 1-3× | hLPO↓, hGSH↑, hGPx/hCAT↑, hMPO↓, hNO↓ | Rats | | |
| Zymosan                | 5-50 mg/kg ip for 1-7× | hLPO↓, hGSH↑, hGPx/hCAT↑, hMPO↓, hNO↓, hNO↓, hTNF-α/hIL-1/hLNO↓, hNEC↑ | Rats, mice | \([120-124]\) |
| Cholestasis            | 11-50 mg/kg ip for 7× | hLPO↓, hGSH↑, hGPx/hCAT↑, hMPO↓, hNO↓, hNO↓, hTNF-α/hIL-1/hLNO↓, hNEC↑ | Rats, mice | \([125-129]\) |
| Ble-duct ligation      | 0.5-100 mg/kg per day ip/po for 1× | hLPO↓, hGSH↑, hGPx/hCAT↑, hMPO↓, hNO↓, hNO↓, hTNF-α/hIL-1/hLNO↓, hNEC↑ | Rats, mice | \([130-134]\) |
| Ionizing radiation     | 0.8-6.0 | hLPO↓, hGSH↑, hGPx/hCAT↑, hMPO↓, hNO↓, hNO↓, hTNF-α/hIL-1/hLNO↓, hNEC↑ | Rats, mice | \([135-139]\) |
| Malaria                | Schistosoma mansoni | 10 mg/kg per day ip for 30 d | hLPO↓, hGSH↑, hGPx/hCAT↑, hMPO↓, hNO↓, hNO↓, hTNF-α/hIL-1/hLNO↓, hNEC↑ | Rats, mice | \([140-143]\) |

†: Upregulation/increase/improvement; ↓: Downregulation/decrease/deterioration; ALT: Alanine transaminase; ALP: Alkaline phosphatase; AST: Aspartate transaminase; BCCG: Bacillus Calmette-Guérin; BL: 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; hHSO: Hepatic heat shock protein; hHO-1: Hepatic heme oxygenase 1; hIL: Hepatic interleukin; hNO: Hepatic nitric oxide; hNEC: Hepatic necrosis; hSOD: Hepatic superoxide dismutase; hTNF-α: Hepatic tumor necrosis factor α; hXO: Hepatic xanthine oxidase; ig: Intragastrically; ip: Intrapertioneally; iv: Intravenously; LD: Lethal dose; LPS: Lipopolysaccharide; MAP: Mean arterial pressure; PDR-ICG: Plasma disappearance rate of indocyanine green; po: Per os; sc: Subcutaneously.
vestigators also report an increase in hepatic catalase after melatonin treatment\[44-71,78-83,89,90,108,111,115,116,118,125,132,145,159\].

**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\[80-82,86,87,90,92,94-96,98-103,111-114,116-120,125-127,130-146\]. 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\[85,87,108,109,111,134,143\].

**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-k-light-chain-enhancer of activated B cells\[42,43,53,62,80,99\]. This was demonstrated in sepsis and after ischemia/reperfusion, as well as after carbon tetrachloride and dimethylhydrosulfoxime 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\[41-43,49,53,60,68,81,146\].

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 rats\[148\]. El-Sokkary et al\[150\] 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 MT1 and MT2 (previous terminology: Mel1a and Mel1b, 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 adenylyl cyclases, phospholipase A2 and C, and calcium and potassium channels\[154-159\]. A third receptor, named MT3, was demonstrated to be equivalent to intracellular quinolone-reductase-2\[160\]. Non-mammalian species express yet another receptor subtype named Mel2b, which is the first type of melatonin receptor to be discovered\[161\].

In the liver, the presence of MT1, MT2 and MT3 has been reported in various species\[141-171\]. 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        | [169.170] |
| C3H/He mouse             | +   | +   | NT      | RT-PCR        | [144] |
| Swiss mouse              | +   | -   | NT      | RT-PCR        | [144] |
| Sprague-Dawley rat       | -   | +   | NT      | RT-PCR        | [144] |
| Golden rabbitfish        | +   | +   | NT      | RT-PCR        | [166,167] |
| European sea bass        | -   | +   | NT      | RT-PCR        | [144] |
| Senegalese sole          | +   | -   | NT      | RT-PCR        | [144] |
| Syrian hamster           | NT  | NT  | +  iodine ligand | [163,164] |
| 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 detected; RT-PCR: Reverse transcription-polymerase chain reaction.

An 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 MT1 or MT2 receptors in humans. Some evidence points to the possibility that melatonin receptor expression may exhibit circadian variations; this has also been demonstrated for hepatic MT1 and MT2.[163,164-168] 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 MT1 and MT2 receptors.[154]. Only a few publications have demonstrated data on the MT1 or MT2 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 MT1 in the liver.[173]. It appeared that MT1 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 perportal 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 MT1 expression might allow the preferential protection of centrilobular 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.[165,166-168]. 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. Most certainly, melatonin has a profound influence on hepatocellular gene expression; this has been demonstrated in heat shock protein expression by various investigators. 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. 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, 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. 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 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 Vaitetti has already demonstrated in two studies that melatonin may reduce cold ischemic injury in rat liver, 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. 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.

ACKNOWLEDGMENTS

The author would like to thank Dr. Larsen R, Professor, Dr. Rensing H, Professor, Dr. Volk T, Professor, Fink T and Wolf B for their encouragement and support.

REFERENCES

1. Reiter RJ, Tan DX, Manchester LC, Pilar Terron M, Flores LJ, Koppipse S. Medical implications of melatonin: receptor-mediated and receptor-independent actions. Adv Med Sci 2007; 52: 11-28
2. Pandi-Perumal SR, Srinivasan V, Maestroni GJ, Cardinali DP, Poeggeler B, Hardeland R. Melatonin: Nature’s most versatile biological signal? FEBS J 2006; 273: 2813-2838
3. Doolen S, Krause DN, Dubocovich ML, Duckles SP. Melatonin mediates two distinct responses in vascular smooth muscle. Eur J Pharmacol 1998; 345: 65-69
4. Ting KN, Dunn WR, Davies DJ, Sugden D, Delagrange P, Guardiola-Lemaître B, Scalbert E, Wilson VG. Studies on the vasoconstrictor action of melatonin and putative melatonin receptor ligands in the tail artery of juvenile Wistar rats. Br J Pharmacol 1997; 122: 1299-1306
5. Viswanathan M, Laitinen JT, Saavedra JM. Expression of melatonin receptors in arteries involved in thermoregulation. Proc Natl Acad Sci USA 1990; 87: 6200-6203
6. Arendt J. Melatonin and the pineal gland: influence on mammalian seasonal and circadian physiology. Rev Reprod 1998; 3: 13-22
7. Korf HW, Schomerus C, Stehle JH. The pineal organ, its hormone, melatonin, and the photoneuroendocrine system. Adv Anat Embryol Cell Biol 1998; 146: 1-100
8. Klein DC, Moore RY. Pineal N-acetyltransferase and hydroxyindole-O-methyltransferase: control by the retinohypothalamic tract and the suprachiasmatic nucleus. Brain Res 1979; 174: 245-262
9. Reppert SM, Weaver DR. Coordination of circadian timing in mammals. Nature 2002; 415: 935-941
10. Sugden D. Melatonin biosynthesis in the mammalian pineal gland. Experientia 1989; 45: 922-932
11. Goldman BD. Mammalian photoperiodic system: formal properties and neuroendocrine mechanisms of photoperiodic time measurement. J Biol Rhythms 2001; 16: 283-301
12. Reiter RJ. The melatonin rhythm: both a clock and a calendar. Experientia 1993; 49: 654-664
13. Reiter RJ. The pineal and its hormones in the control of reproduction in mammals. Endocr Rev 1980; 1: 109-131
14. Lincoln GA, Andersson H, Hazlerigg D. Clock genes and the long-term regulation of prolactin secretion: evidence for a photoperiod/circannual timer in the pars tuberalis. J Neuroendocrinol 2003; 15: 390-397
15. Niklowitz P, Lerchl A, Nieschlag E. Photoperiodic responses in Djungarian hamsters (Phodopus sungorus): importance of light history for pineal and serum melatonin profiles. Biol Reprod 1994; 51: 714-724
16. Tosini G, Menaker M. The clock in the mouse retina: melatonin synthesis and photoreceptor degeneration. Brain Res 1998; 789: 221-228
17. Conti A, Conconi S, Hertens E, Skwarlo-Sonta K, Markowska M, Maestroni JM. Evidence for melatonin synthesis in mouse and human bone marrow cells. J Pineal Res 2000; 28: 193-202
18. Slominski A, Tobin DJ, Zmięwski MA, Wortzman J, Paus R. Melatonin in the skin: synthesis, metabolism and functions. Trends Endocrinol Metab 2008; 19: 17-24
19. Djeridane Y, Thouitou Y. Melatonin synthesis in the rat hardier gland: age- and time-related effects. Exp Eye Res 2001; 72: 487-492
20. Champier J, Claustret B, Besançon R, Eymyn C, Keller C, Jouvet A, Chamba G, Fève-Montagne M. Evidence for tryptophan hydroxylase and hydroxy-indol-O-methyl-transferase mRNAs in human blood platelets. Life Sci 1997; 60: 2191-2197
21. Carrillo-Vico A, Calvo JR, Abreu F, Lardone PJ, García-Mau-
expression of the inducible NO synthase II in liver and lung and prevents endotoxemia in lipopolysaccharide-induced multiple organ dysfunction syndrome in rats. FASEB J 1999; 13: 1537-1546.

Sener G, Toklu H, Kapucu C, Eroan F, Erkanli G, Kaçmaz A, Tilkı M, Yeğen BC. Melatonin protects against oxidative organ injury in a rat model of sepsis. Surg Today 2005; 35: 52-59.

Carrillo-Vico A, Lardone PJ, Naji L, Fernández-Santos JM, Martín-Lacave I, Guerrero JM, Calvo JR. Beneficial pleiotropic actions of melatonin in an experimental model of septic shock in mice: regulation of pro-/anti-inflammatory cytokine network, protection against oxidative damage and anti-apoptotic effects. J Pineal Res 2005; 39: 401-408.

Wu CC, Chiao CW, Hsiao G, Chen A, Yen MH. Melatonin prevents endotoxin-induced circulatory failure in rats. J Pineal Res 2001; 30: 147-156.

Xu DX, Wei W, Sun MF, Wei LZ, Wang JP. Melatonin attenuates lipopolysaccharide-induced down-regulation of pregnancy X receptor and its target gene CYP3A in mouse liver. J Pineal Res 2005; 38: 27-34.

Sewerynek E, Abe M, Reiter RJ, Barlow-Walden LR, Chen L, McCabe TJ, Roman Lj, Diaz-Lopez B. Melatonin administration prevents lipopolysaccharide-induced oxidative damage in phenobarbital-treated animals. J Cell Biochem 1995; 58: 436-444.

Sewerynek E, Melchiiorri D, Reiter RJ, Ortiz GG, Lewinski A. Lipopolysaccharide-induced hepatotoxicity is inhibited by the antioxidant melatonin. Eur J Pharmacol 1995; 293: 327-334.

Wang H, Wei W, Shen YX, Dong C, Zhang LS, Wang NP, Yue L, Xu SY. Protective effect of melatonin against liver injury in mice induced by Bacillus Calmette-Guerin plus lipopolysaccharide. World J Gastroenterol 2004; 10: 2690-2696.

Wang H, Xu DX, Lv JW, Ning H, Wei W. Melatonin attenuates lipopolysaccharide (LPS)-induced apoptotic liver damage in D-galactosamine-sensitized mice. Toxicology 2007; 237: 49-57.

Wu JY, Tsou MY, Chen TH, Chen SJ, Tsao CM, Wu CC. Therapeutic effects of melatonin on peritonitis-induced septic shock with multiple organ dysfunction syndrome in rats. J Pineal Res 2008; 45: 106-116.

Mathes AM, Kubuls D, Pradaruitti S, Bentley A, Weiler J, Wolf B, Ziegeler S, Bauer I, Rensing H. Melatonin pretreatment improves liver function and hepatic perfusion after hemorrhagic shock. Shock 2008; 29: 112-118.

Mathes AM, Kubuls D, Weiler J, Bentley A, Waibel L, Wolf B, Rensing H. Melatonin receptors mediate improvements of liver function but not of hepatic perfusion and integrity after hemorrhagic shock in rats. Crit Care Med 2008; 36: 24-29.

Yang FL, Suebq YM, Lee CJ, Lee RP, Peng TC, Hsu BG. Melatonin Ameliorates Hemorrhagic Shock-Induced Organ Damage in Rats. J Surg Res 2009; Epub ahead of print.

Rodríguez-Reynoso S, Leal C, Portilla E, Olivares N, Mutiz J. Effect of exogenous melatonin on hepatic energetic status during ischemia/reperfusion: possible role of tumor necrosis factor-alpha and nitric oxide. J Surg Res 2001; 100: 141-149.

Bülbüller N, Çetinkaya Z, Akkus MA, Cifter C, İlhan YS, Dogru O, Aygen E. The effects of melatonin and prostaglandin E1 analogue on experimental hepatic ischaemia reperfusion damage. Int J Clin Pract 2003; 57: 857-860.

Sener G, Tosun O, Sehirli AO, Kaçmaz A, Arbak S, Ersoy Y, Ayanoglu-Dülger G. Melatonin and N-acetyl-cysteine have beneficial effects during hepatic ischemia and reperfusion. Life Sci 2003; 72: 2707-2718.

Zhang WH, Li JY, Zhou Y. Melatonin abates liver ischemia/reperfusion injury by improving the balance between nitric oxide and endothelin. Hepatobiliary Pancreat Dis Int 2006; 5: 574-579.

Park SW, Choi SM, Lee SM. Effect of melatonin on altered expression of vasoregulatory genes during hepatic ischemia/
reperfusion. Arch Pharm Res 2007; 30: 1619-1624

Sewerynek E, Reiter RJ, Melchiorri D, Ortiz GG, Lewinski A. Oxidative damage in the liver induced by ischemia-reperfusion: protection by melatonin. Hepatogastroenterology 1996; 43: 898-902

Kim SH, Lee SM. Cytotoxic effects of melatonin against necrosis and apoptosis induced by ischemia/reperfusion injury in rat liver. J Pineal Res 2008; 44: 165-171

Liang R, Nickkholgh A, Hoffmann K, Kern M, Schneider H, Sobirey M, Zorn M, Büchner MW, Schenmer P. Melatonin protects from hepatic reperfusion injury through inhibition of JNK and JNK pathways and modulation of cell proliferation. J Pineal Res 2009; 46: S14

Baykara B, Tekmen I, Pekcetin C, Ulukus C, Tuncel P, Sagol O, Ormen M, Ozogul C. The protective effects of carnosine and melatonin in ischemia-reperfusion injury in the rat liver. Acta Histochem 2009; 111: 42-51

Li JY, Yin HZ, Gu X, Zhou Y, Zhang WH, Qin YM. Melatonin protects liver from intestine ischemia reperfusion injury in rats. World J Gastroenterol 2008; 14: 7392-7396

Kirimlioglu H, Ecevit A, Yilmaz S, Kirimlioglu V, Karabulut AB. Effect of resveratrol and melatonin on oxidative stress enzymes, regeneration, and hepatocyte ultrastructure in rats subjected to 70% partial hepatectomy. Transplant Proc 2008; 40: 285-289

Carneiro RC, Reiter RJ. Delta-aminolevulinic acid-induced lipid peroxidation in rat kidney and liver is attenuated by melatonin: an in vitro and in vivo study. J Pineal Res 1999; 24: 131-136

Karbowinski M, Reiter RJ, Garcia JJ, Tan DX, Qi W, Manchester LC. Melatonin reduces rat hepatic macromolecular damage due to oxidative stress caused by delta-aminolevulinic acid. Biochem Biophys Acta 2000; 1523: 140-146

Matsura T, Nishida T, Togawa A, Horie S, Kusumoto C, Ohata S, Nakada J, Ishibe Y, Yamada K, Ohta Y. Mechanisms of protection by melatonin against acetaminophen-induced protection of liver in mice. J Pineal Res 2006; 41: 211-219

Sener G, Sehirli AO, Ayanoglu-Dulger G. Protective effects of melatonin, vitamin E and N-acetylcysteine against acetaminophen toxicity in mice: a comparative study. J Pineal Res 2003; 35: 61-68

Kanno S, Tomizawa A, Hiura T, Osanai Y, Kakuta M, Kita-jima Y, Koivsai K, Ohtake T, Ujibe M, Ishikawa M. Melatonin protects on toxicity by acetaminophen but not on pharmacological effects in mice. Biol Pharm Bull 2006; 29: 472-476

Catala A, Aybar A, Puskas LG, Kitajka K. Melatonin-induced gene expression changes and its preventive effects on adriamycin-induced lipid peroxidation in rat liver. J Pineal Res 2007; 42: 43-49

Rapozzi V, Comelli M, Mavelli I, Sentjurc M, Schara M, Peris-lin S, Giraldel T. Melatonin and oxidative damage in mice liver induced by the prooxidant antitumor drug, adriamycin. In Vitro 1999; 13: 45-50

Obhan AM, El-Massry MA, Amer MA, Arafa M. Melatonin controls oxidative stress and modulates iron, ferritin, and transferrin levels in adriamycin treated rats. Life Sci 2008; 83: 563-568

Meki AR, Abdel-Ghaffar SK, El-Gibaly I. Aflatoxin B1 induces apoptosis in rat liver: protective effect of melatonin. Neuro Endocrinol Lett 2001; 22: 417-426

Meki AR, Esmail Eel-D, Hussein AA, Hassanein HM. Caspase-3 and heat shock protein 70 in rat liver treated with aflatoxin B1: effect of melatonin. Toxicon 2004; 43: 93-100

Gesening A, Karbowkorn-Lewinska M. Protective effects of melatonin and N-acetylcysteirontin on aflatoxin B1-induced lipid peroxidation in rats. Cell Biochem Funct 2008; 26: 314-319

Ozgen H, Karaman M, Cigremis Y, Tuzcu M, Ozkan K, Erdag D. Effectiveness of melatonin on aflatoxicosis in chicks. Res Vet Sci 2009; 86: 485-489

Sirajudeen M, Gopi K, Tyagi JS, Moudgal RP, Mohan J, Singh R. Protective effects of melatonin in reduction of oxidative damage and immunosuppression induced by aflatoxin B(1)-contaminated diets in young chicks. Environ Toxicol 2009; Epub ahead of print

Sigala F, Theocharis S, Sigalas K, Markantonis-Kyroudis S, Papalabros E, Triantafyllou A, Kostopanagiotou G, Andreadou I. Therapeutic value of melatonin in an experimental model of liver injury and regeneration. J Pineal Res 2006; 40: 270-279

Pal S, Chatterjee AK. Possible beneficial effects of melatonin supplementation on arsenic-induced oxidative stress in Wistar rats. Drug Chem Toxicol 2006; 29: 423-433

Kim CY, Lee MJ, Lee SM, Lee WC, Kim JS. Effect of melatonin on cadmium-induced hepatotoxicity in male Sprague-Dawley rats. Tohoku J Exp Med 1998; 186: 205-213

Eybi V, Kotyzova D, Koutensky J. Comparative study of natural antioxidants - curcumin, resveratrol and melatonin - in cadmium-induced oxidative damage in mice. Toxicology 2006; 225: 150-156

Kara H, Cevik A, Konar V, Dayangac A, Servi K. Effects of selenium with vitamin E and melatonin on cadmium-induced oxidative damage in rat liver and kidneys. Biol Trace Elem Res 2008; 125: 236-244

El-Sokkary GH, Nafady AA, Shabash EH. Melatonin administration ameliorates cadmium-induced oxidative stress and morphological changes in the liver of rat. Ecotoxocol Environ Saf 2010; 73: 456-463

Ohya Y, Kongo M, Sasaki E, Nishida K, Ishiguro I. Therapeutic effect of melatonin on carbon tetrachloride-induced acute liver injury in rats. J Pineal Res 2000; 28: 119-126

Ohya Y, Kongo-Nishiuma M, Matsura T, Yamada K, Kitagawa A, Kishikawa T. Melatonin prevents disruption of hepatic reactive oxygen species metabolism in rats treated with carbon tetrachloride. J Pineal Res 2004; 36: 10-17

Ohya Y, Kongo M, Sasaki E, Nishida K, Ishiguro I. Preventive effect of melatonin on the progression of carbon tetrachloride-induced acute liver injury in rats. Adv Exp Med Biol 1999; 467: 327-332

Kus I, Ogeturk M, Oner H, Sahin S, Yekeler H, Sarsilmaz M. Protective effects of melatonin against carbon tetrachloride-induced hepatotoxicity in rats: a light microscopic and biochemical study. Cell Biochem Funct 2005; 23: 169-174

Zavodnik LB, Zavodnik IB, Lapshina EA, Belonovskaya EB, Martinchik DJ, Kravchuk RI, Bryszewska M, Reiter RJ. Protective effects of melatonin against carbon tetrachloride hepatotoxicity in rats. Cell Biochem Funct 2005; 23: 353-359

Wang H, Wei W, Wang NP, Gui SY, Wu L. Sun WY, Xu SY. Melatonin ameliorates carbon tetrachloride-induced hepatic fibrogenesis in rats via inhibition of oxidative stress. Life Sci 2005; 77: 1902-1915

Noyan T, Kömüroğlu U, Bayram I, Sekeroğlu MR. Comparison of the effects of melatonin and pentoxifylline on carbon tetrachloride-induced liver toxicity in mice. Cell Bio Chem 2006; 22: 381-391

Ogeturk M, Kus I, Pekmez H, Yekeler H, Sahin S, Sarsilmaz M. Inhibition of carbon tetrachloride-mediated apoptosis and oxidative stress by melatonin in experimental liver fibrosis. Toxicol Ind Health 2008; 24: 201-208

Hong RT, Xu JM, Mei Q. Melatonin ameliorates experimental hepatic fibrosis induced by carbon tetrachloride in rats. World J Gastroenterol 2009; 15: 1452-1458

Shaker ME, Houssein ME, Abo-Hashem EM, Ibrahim TM. Comparison of vitamin E, L-carnitine and melatonin in ameliorating carbon tetrachloride and diabetes induced hepatic oxidative stress. J Physiol Biochem 2009; 65: 225-233

Manda K, Bhatia AL. Prophylactic action of melatonin against cyclophosphamide-induced oxidative stress in mice. Cell Bio Chem 2003; 19: 367-372

Kwak CS, Mun KC. The beneficial effect of melatonin for cyclosporine hepatotoxicity in rats. Transplant Proc 2000; 32: 898-902
Mathes AM. Photoprotective actions of melatonin

135 Padillo FJ, Cruz A, Navarrete C, Bujalance I, Briceno J, Galardo JL, Marchal T, Caballero R, Tünezi I, Muntané J, Montilla P, Pera-Madrazo C. Melatonin prevents oxidative stress and hepatocyte cell death induced by experimental cholestasis. Free Radic Res 2006; 38: 697-704

136 Esrefoglu M, Gül M, Emre MH, Polat A, Selimoglu MA. Protective effect of low dose of melatonin against cholestatic oxidative stress after common bile duct ligation in rats. World J Gastroenterol 2005; 11: 1951-1956

137 Ohta Y, Imai Y, Matsura T, Yamada K, Tokunaga K. Succes postadministration melatonin prevents disruption of hepatic antioxidant status in rats with bile duct ligation. J Pineal Res 2008; 45: 267-274

138 Muñoz-Castañeda JR, Tünezi I, Herencia C, Ranchal I, González R, Ramirez LM, Arjona A, Barcos M, Espejo I, Cruz A, Montilla P, Padillo FJ, Muntané J. Melatonin exerts a more potent effect than S-adenosyl-l-methionine against iron metabolism disturbances, oxidative stress and tissue injury induced by obstructive jaundice in rats. Chem Biol Interact 2008; 179: 79-87

139 Emre MH, Polat A, Esrefoglu M, Karabulut AB, Gül M. Effects of melatonin and acetylalicylic acid against hepatic oxidative stress after bile duct ligation in rat. Acta Physiol Hung 2008; 95: 349-363

140 Huang LT, Tiao MM, Tain YL, Chen CC, Hsieh CS. Melatonin ameliorates bile duct ligation-induced systemic oxidative stress and spatial memory deficits in developing rats. Pediatr Res 2009; 65: 176-180

141 Barbownik M, Reiter RJ, Qi W, García JJ, Tan DX, Manchester LC, Vijayalaxmi. Protective effects of melatonin against oxidation of guanine bases in DNA and decreased microsomal membrane fluidity in rat liver induced by whole body ionizing radiation. Mol Cell Biochem 2000; 211: 137-144

142 Taysi S, Koc M, Büyükkokulu ME, Altinkaynak K, Sahin YN. Melatonin reduces lipid peroxidation and nitric oxide production during irradiation-induced oxidative injury in the rat liver. J Pineal Res 2003; 34: 173-177

143 Sener G, Jahovic N, Tosunc O, Atasoy BM, Yeğen BC. Melatonin ameliorates ionizing radiation-induced oxidative organ damage in rats. Life Sci 2003; 74: 563-572

144 Koc M, Taysi S, Büyükkokulu ME, Bakan N. Melatonin protects rat liver against irradiation-induced oxidative injury. J Radiat Res (Tokyo) 2003; 44: 211-215

145 El-Missiry MA, Fayed TA, El-Sawy MR, El-Sayed AA. Ameliorative effect of melatonin against gamma-irradiation-induced oxidative stress and tissue injury. Ecotoxicol Environ Saf 2007; 66: 278-286

146 El-Sokkary GH, Omar HM, Hassanein AF, Cuzzocrea S, Reiter RJ. Melatonin reduces oxidative damage and increases survival of mice infected with Schistosoma mansoni. Free Radic Biol Med 2002; 32: 319-332

147 Yan J, Shen F, Wang K, Wu MC. Patients with advanced primary hepatocellular carcinoma treated by melatonin and transcatheter arterial chemoembolization: a prospective study. Hepatobiliary Pancreat Dis Int 2002; 1: 183-186

148 Daniels WM, Reiter RJ, Melchiorri D, Sewerynek E, Pablos A, Ortiz GG. Melatonin counteracts lipid peroxidation induced by carbon tetrachloride but does not restore glucose-6-phosphatase activity. J Pineal Res 1995; 19: 1-6

149 Kim SJ, Reiter RJ, Rouvier Garay MV, Qi W, El-Sokkary GH, Tan DX, 2-Nitropropane-induced lipid peroxidation: antioxidant effects of melatonin. Toxicology 2004; 193: 183-190

150 Genc S, Girgili F, Oner-Iyidoğan Y, Onaran I. The effect of melatonin administration on ethanol-induced lipid peroxidation in rats. Pharmacolet Res 1998; 37: 37-40

151 El-Sokkary GH, Reiter RJ, Tan DX, Kim SJ, Cabrera J. Inhibitory effect of melatonin on products of lipid peroxidation resulting from chronic ethanol administration. Alcohol Alcohol 1999; 34: 842-850

152 Hu S, Yin S, Jiang X, Huang D, Shen G. Melatonin protects against alcoholic liver injury by attenuating oxidative stress, inflammatory response, and apoptosis. Eur J Pharmacol 2009; 616: 287-292

153 Dubovcik ML, Rivera-Bermudez MA, Gerdin MJ, Mansan MI. Molecular pharmacology, regulation and function of mammalian melatonin receptors. Front Biosci 2003; 8: d1093-d1108

154 Jockers R, Maurice P, Boutin JA, Delargrange P. Melatonin receptors, heterodimerization, signal transduction and binding sites: what's new? Br J Pharmacol 2008; 154: 1182-1195

155 von Gall C, Stehle JH, Weaver DR. Mammalian melatonin receptors: molecular biology and signal transduction. Cell Tiss Res 2002; 309: 151-162

156 New DC, Tsim ST, Wong YH. G protein-linked effector and second messenger systems involved in melatonin signal transduction. Neurosignals 2003; 12: 59-70

157 Pandi-Perumal SR, Trakt I, Srinivasan V, Spence DW, Maestro GJ, Zisapel N, Cardinale DP. Physiological effects of melatonin: role of melatonin receptors and signal transduction pathways. Prog Neurobiol 2008; 85: 335-353

158 Barrett P, Morris M, Choi WS, Ross A, Morgan PJ. Melatonin receptors and signal transduction mechanisms. Biol Signals Recept 1999; 8: 6-14

159 Nosjean O, Ferro M, Coge F, Beauverger P, Henlin JM, Lefoulon F, Fauchere JL, Delargrange P, Canet E, Boutin JA. Identification of the melatonin-binding site MT3 as the quisaine reductase 2. J Biol Chem 2000; 275: 31311-31317

160 Ebisawa T, Karne S, Lerner MR, Reppert SM. Expression cloning of a high-affinity melatonin receptor from Xenopus dermal melanophores. Proc Natl Acad Sci USA 1994; 91: 6133-6137

161 Ishii H, Tanaka N, Kobayashi M, Kato M, Sakuma Y. Gene structures, biochemical characterization and distribution of rat melatonin receptors. J Pineal Res 2009; 59: 37-47

162 Sánchez-Hidalgo M, Guerrero Montávez JM, Carrascosa-Salomón Mdél P, Naranjo Gutierrez Mdél C, Lardone P, de la Lastra Romero CA. Decreased MT1 and MT2 melatonin receptor expression in extrapinal tissues of the rat during physiological aging. J Pineal Res 2009; 46: 29-35

163 Sallinen P, Saarelä S, Ilves M, Vakkuri O, Leppäluoto J. The expression of MT1 and MT2 melatonin receptor mRNA in several rat tissues. Life Sci 2005; 76: 1123-1134

164 Mühllbauer E, Gross E, Labucay K, Wolgast S, Peschke E. Loss of melatonin signalling and its impact on circadian rhythms in mouse organs regulating blood glucose. Eur J Pharmacol 2009; 606: 61-71

165 Naji L, Carrillo-Vico A, Guerrero JM, Calvo JR. Expression of membrane and nuclear melatonin receptors in mouse peripheral organs. Life Sci 2004; 74: 2227-2236

166 Park YJ, Park JG, Hiyakawa N, Lee YD, Kim SJ, Takemura A. Diurnal and circadian regulation of a melatonin receptor, MT1, in the golden rabbitfish, Siganus guttatus. Gen Comp Endocrinol 2007; 150: 253-262

167 Park YJ, Park JG, Kim SJ, Lee YD, Saydur Rahman M, Takemura A. Melatonin receptor of a reef fish with lunar-related rhythmicity: cloning and daily variations. J Pineal Res 2006; 41: 166-174

168 Sauzet S, Besseau L, Herrera Perez P, Covés D, Chatain B, Peyric E, Beouel G, Muñoz-Cueto JA, Falcón J. Cloning and retinal expression of melatonin receptors in the European sea bass, Dicentrarchus labrax. Gen Comp Endocrinol 2008; 157: 156-195

169 Confente F, Rendón MC, Besseau L, Falcón J, Muñoz-Cueto JA. Melatonin receptors in a pleuronectiform species, Solea senegalensis: Cloning, tissue expression, day-night and seasonal variations. Gen Comp Endocrinol 2010; 167: 202-214

170 Nosjean O, Nicolas JP, Klupsch F, Delargrange P, Canet E, Boutin JA. Comparative pharmacological studies of melatonin receptors: MT1, MT2 and MT3/RQ2. Tissue distribution of MT3/RQ2. Biochem Pharmacol 2001; 61: 1369-1379
Mathes AM. Hepatoprotective actions of melatonin

Brzozowski T, Konturek PC, Zwirska-Korczaka K, Konturek SJ, Brzozowska I, Drozdowicz D, Sliwowski Z, Pawlik M, Pawlik WW, Hahn EG. Importance of the pineal gland, endogenous prostaglandins and sensory nerves in the gastrointestinal actions of central and peripheral melatonin against stress-induced damage. J Pineal Res 2005; 39: 375-385

Witt-Endeber PA, Radio NM, Doctor JS, Davis VL. Therapeutic treatments potentially mediated by melatonin receptors: potential clinical uses in the prevention of osteoporosis, cancer and as an adjuvant therapy. J Pineal Res 2006; 41: 297-305

Mathes A, Ruf C, Fink T, Abend M, Rensing H. Molecular effects of melatonin and ramelteon administration after hemorrhagic shock in rat liver: BAPCPCl-6. Eur J Anaesthesiol 2010; 27: 2

Schemmer P, Nickkolgh A, Schneider H, Sobirey M, Weigand M, Koch M, Weitz J, Büchler MW. PORTAL: pilot study on the safety and tolerance of preoperative melatonin application in patients undergoing major liver resection: a double-blind randomized placebo-controlled trial. BMC Surg 2008; 8: 2