Pharmacological Research 105 (2016) 108–120

Contents lists available at ScienceDirect

Pharmacological Research

journal homepage: www.elsevier.com/locate/yphrs

Review

Melatonin's role in preventing toxin-related and sepsis-mediated hepatic damage: A review

Eduardo Esteban-Zubero[a,*], Moisés Alejandro Alatorre-Jiménez[b], Laura López-Pingarrón[c], Marcos César Reyes-Gonzales[a], Priscilla Almeida-Souza[a], Amparo Cantín-Golet[c], Francisco José Ruiz-Ruiz[c], Dun-Xian Tan[b], José Joaquín García[a], Russel J. Reiter[b,*]

[a] Department of Pharmacology and Physiology, University of Zaragoza, Calle Domingo Miral s/n, 50009, Zaragoza, Spain
[b] Department of Cellular and Structural Biology, University of Texas Health Science Center at San Antonio, 7703 Floyd Curl Drive, San Antonio, TX 78229, USA
[c] Department of Medicine, Psychiatry and Dermatology, University of Zaragoza, Calle Domingo Miral s/n, 50009. Zaragoza, Spain

ARTICLE INFO

Article history:
Received 12 December 2015
Received in revised form 13 January 2016
Accepted 15 January 2016
Available online 22 January 2016

Keywords:
Liver toxicity
Sepsis
Chemotherapeutic
Oxidative stress
Lipid peroxidation
Melatonin

ABSTRACT

The liver is a central organ in detoxifying molecules and would otherwise cause molecular damage throughout the organism. Numerous toxic agents including aflatoxin, heavy metals, nicotine, carbon tetrachloride, thioacetamide, and toxins derived during septic processes, generate reactive oxygen species followed by molecular damage to lipids, proteins and DNA, which culminates in hepatic cell death. As a result, the identification of protective agents capable of ameliorating the damage at the cellular level is an urgent need. Melatonin is a powerful endogenous antioxidant produced by the pineal gland and a variety of other organs and many studies confirm its benefits against oxidative stress including lipid peroxidation, protein mutilation and molecular degeneration in various organs, including the liver. Recent studies confirm the benefits of melatonin in reducing the cellular damage generated as a result of the metabolism of toxic agents. These protective effects are apparent when melatonin is given as a sole therapy or in conjunction with other potentially protective agents. This review summarizes the published reports that document melatonin's ability to protect hepatocytes from molecular damage due to a wide variety of substances (aflatoxin, heavy metals, nicotine, carbon tetrachloride, chemotherapeutics, and endotoxins involved in the septic process), and explains the potential mechanisms by which melatonin provides these benefits. Melatonin is an endogenously-produced molecule which has a very high safety profile that should find utility as a protective molecule against a host of agents that are known to cause molecular mutilation at the level of the liver.

© 2016 Elsevier Ltd. All rights reserved.

Contents

* Corresponding author.
E-mail addresses: eezubero@gmail.com (E. Esteban-Zubero), reiter@uthscsa.edu (R.J. Reiter).

http://dx.doi.org/10.1016/j.phrs.2016.01.018
1043-6618/© 2016 Elsevier Ltd. All rights reserved.

1. Introduction

Melatonin (*N*-acetyl-5-methoxytryptamine) is a powerful antioxidant produced by the pineal gland as well as numerous organs including ovary, testes, bone marrow, gut, placenta, liver [1–4] (Fig. 1). Initially, melatonin was considered to be exclusively a circadian cycle regulator [5], but numerous studies have documented its activity as a free radical scavenger [6–8] and antioxidant agent [9,10].

Superoxide ($O_2^{\bullet -}$), hydrogen peroxide (H_2O_2), and the hydroxyl radical ($^{\bullet}OH$) are common reactive oxygen species (ROS). They are generated during normal intracellular metabolism, especially in mitochondria and peroxisomes, and by a variety of cytosolic enzyme systems including NADPH oxidase or cytochrome P450 [11]. Nitric oxide ($NO^{\bullet}$) and peroxynitrite ($ONOO^-$) are reactive nitrogen species (RNS) [12]. High concentrations of these substances induce apoptosis and cell death through a process that involves lipid peroxidation (LPO), which causes cell edema due to a disruption of normal fluidity and permeability of cell membranes, massive overload of Ca^{2+} and Na^+, and discharge of cytochrome c (cyt c) into the cytoplasm with the subsequent activation of caspase activity. Some of the major products of LPO are malondialdehyde (MDA) and 4-hydroxynoneal (4-HNE) [13]. Melatonin prevents the peroxidation of lipids, preserves membrane physiology and limits the consequential metabolic disturbances [14].

Melatonin also has indirect means of reducing oxidative damage via stimulating the cellular antioxidant defense system by increasing mRNA levels and the activities of several important antioxidant enzymes including superoxide dismutase (SOD, which catalyzes the conversion of $O_2^{\bullet -}$ to H_2O_2), glutathione peroxidase (GPx), and glutathione reductase (GRd), and promoting the synthesis of another important intracellular antioxidant; glutathione (GSH). Catalase (CAT), also is stimulated by melatonin and causes a direct breakdown of H_2O_2 to O_2 and H_2O [9,15]. Moreover, melatonin inhibits inducible nitric oxide synthase (iNOS), which is involved in $NO^{\bullet}$ generation [16–18].

Mitochondria also are targets of oxidative damage and melatonin protects these essential organelles and improves mitochondrial function via its antioxidant actions and by increasing the activity of mitochondrial electron transport chain (ETC) complexes thereby improving mitochondrial respiration and ATP production [19]. These processes are normally disturbed due to ROS/RNS damage which promotes electron leakage [20]

During LPO, an innate immune response takes place leading to the increased levels of cytokines (IL, TNF-α), which are codified by genes regulated by nuclear transcription factor kB (NF-kB) (e.g. iNOS and COX-2). Melatonin is known to reduce the NF-kB activation [21–24].

The purpose of this review is analyze the generated hepatic damage due to a variety of substances (aflatoxin, heavy metals, nicotine, carbon tetrachloride, chemotherapeutics, and endotoxins involved in sepsis process), and explain how melatonin provides protective actions due to its ability to detoxify ROS/RNS.

2. Aflatoxin and melatonin

Aflatoxins are a group of toxic fungal metabolites that are commonly found in a variety of agriculture products; they have genotoxic, teratogenic, immunotoxic, and carcinogenic effects on animals and humans and are a major concern for companies which work with the associated agricultural products [25,26]. Aflatoxin B1 (AFB1), a metabolite of *Aspergillus flavus*, is a highly potent hepatotoxin and hepatocarcinogen after its activation by the hepatic cytochrome P-450-dependent polysubstrate monooxygenase enzyme superfamily (CYP-450s) [27]. Its final metabolite (AFB1-8,9-epoxide) reacts with DNA due to the generation of ·OH and H_2O_2 and a reduction in the action of SOD, catalase and GPx [28]. Furthermore, $^{\bullet}OH$ alters cellular homeostasis leading to fatty accumulation and degeneration of the liver [29]. These processes, combined with the effects of NO·[30], the action of caspase-3 [31], and HSP70 (a heat shock protein involved in protecting cells from stress damage) [32], induce apoptotic cell death. Additionally, microsomal prostaglandin H synthase (PHS) and cytosolic lipoxygenases are involved in the bioactivation of AFB1 to its electronic DNA binding form[33].

Antioxidant enzymes including SOD, CAT and GPx which are reduced during AFB1-induced oxidative damage, prevent hepatocyte death [34]. Moreover, melatonin, due to its antioxidant actions, reduces liver injury produced by aflatoxin. Awney et al [35]. in a rat model, investigated the action of melatonin as a free radical scavenger on the production of the hepatic H_2O_2 generated during the metabolic activation of AFB1 by rat liver microsomes. The results of this work documented a reduction in H_2O_2 levels in melatonin-treated animals (0.2 mg/kg) without an elevation in cytochrome P-450, which was found to lower after aflatoxin administration. Thus, melatonin was observed to have a protective effect against aflatoxin toxicity, but the molecular pathways involved remain unknown [36].

Meki et al [37]. using a rat model, observed that caspase-3 activity levels were positively correlated with lipid breakdown while negatively correlated with GSH levels. Melatonin administration (5 mg/kg) was associated with a decrease of caspase-3 activity levels, lipid peroxidation product levels, and HSP70 expression while GSH and GPx levels were significantly increased relative to control values. However, the influence of HSP70 is controversial since one previous study agreed with this finding [38], but others reported a negative correlation between HSP70 expression and apoptosis [39,40].

The $^{\bullet}OH$ induces fatty accumulation in the liver while melatonin reduces this response [41]. Ozen et al [42]. using an avian model, observed that the immunoreactivity in aflatoxin plus melatonin treated animals (10 mg/kg orally) compared to aflatoxin chicks was weak, suggesting a scavenger effect of melatonin against ROS and RNS. Moreover, GSH levels were increased and MDA levels fell due to melatonin treatment. Melatonin also stimulated other endogenous antioxidants such as SOD and CAT [43]. In addition, Sirajudeen et al [43] observed an elevation in aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels due to aflatoxicosis in melatonin treated (40 mg/kg orally) versus non-treated chicks.

It was also observed that melatonin's beneficial effects were improved using a buoyant dosage form [44]. The authors used chitosan, a natural polysaccharide, due to its characteristics to prolong the gastric residence time of active components, ensure slow delivery of the drug from its absorption site, and reduce the variability of transit performance [45].

Melatonin's beneficial effects also have been compared with those of *N*-acetylserotonin (NAc-5HT) [46]. an immediate precursor of melatonin with well known antioxidant actions [47]. In this

Download English Version:

https://daneshyari.com/en/article/2562036

Download Persian Version:

https://daneshyari.com/article/2562036

Daneshyari.com