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Review Article

Melatonin and Oxidative Liver Damage during Ischemia-Reperfusion

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Abstract

Melatonin is a hormone released by the pineal gland with powerful antioxidant activity. Many studies shown protective effect of melatonin on ischemia-reperfusion injury (IRI) in different organs. In this article we analyzed literature and own data about mechanisms of melatonin influence on oxidative liver damage during ischemia-reperfusion.

Keywords: *Melatonin; Oxidative Stress; Liver; Ischemia-Reperfusion*

Introduction

Oxidative stress is a basic mechanism of hepatocyte damage in liver ischemia-reperfusion syndrome [1]. Reactive oxygen species (ROS) are produced by tissues during ischemia; however, after reperfusion, their generation sharply increases. Hydroxyl radical (HO*-), superoxide anion-radical (O_2^{*-}) and hydrogen hydroperoxide (H_2O_2) contribute to mitochondrial dysfunction, chemotaxis, lipid peroxidation (LPO), disintegration of proteins and cell membranes. In addition, ROS can cause damage and dysfunction of the endothelium, disrupting the processes of microcirculation in the liver after ischemia [2]. During ischemia, the breakdown of adenosine-3-phosphate (ATP) leads to the accumulation of hypoxanthine. Simultaneously, xanthine dehydrogenase is converted into xanthine oxidase, which decomposes hypoxanthine into O_2^{*-}, H_2O_2 and uric acid salt under reoxygenation conditions. Therefore, liver reperfusion inevitably leads to oxidative stress.

Nature and biology of melatonin

Melatonin, N-acetyl-5-methoxytryptamine, is a hormone of the pineal gland that regulates many biological functions, the main of which are participation in the circadian rhythms of the body and protection of cells from oxidative stress [3]. The source for the synthesis of melatonin, as well as for vitamin B3, is the amino acid tryptophan. Being subjected to decarboxylation, this amino acid is converted into the neurotransmitter serotonin, after which melatonin is formed under the influence of N-acetyltransferase. Most of the biological effects of melatonin are mediated through the activation of specific membrane receptors to it of the 1st (MT-1) and 2nd (MT-2) types, which react with the hormone at pico- and nanomolar concentrations, respectively [4]. These receptors belong to a separate group of the superfamily of membrane-integrated G-proteins that carry phosphorylation sites for protein kinases C and A. The effector link of melatonin receptors includes adenylate cyclase, phospholipase C, phospholipase A2, potassium channels, etc [5]. MT-1 and MT-2 are found in the hypothalamus, pituitary, cerebral cortex, adrenal glands, retina, heart, lungs, kidneys, liver, intestines, arteries, blood cells, etc. which determines the breadth of its regulatory effects in the body [6]. It is interesting to note that, interacting with MT-1, melatonin causes anticonvulsant and vasoconstrictor effects, and with MT-2 it causes vascular vasodilation. In addition to membrane receptors, specific nuclear receptors for

melatonin NR1F, belonging to the family of steroid-thyroid receptors (RZR/ROR), have also been identified. Activation of the latter leads to an increase in the expression of antioxidant enzymes, such as SOD, glutathione peroxidase, glutathione reductase, catalase, and has immunomodulatory and antitumor effects [6]. Moreover, it has been shown *in vitro* that melatonin is able to act as a direct ROS quencher (O_2^{*-}, HO*-, NO), moreover, it is 2 times more effective than α-tocopherol [7]. According this data, it was detected that melatonin reduces the degree of reperfusion damage to the heart, lungs, and kidneys [8].

The role of melatonin in hepatic ischemia-reperfusion injury

The role of melatonin in liver pathology remains controversial. Despite the large number of works proving the protective role of melatonin in oxidative damage to the organ, it should be noted that there are reports that do not confirm the hepatoprotective effect of the pineal gland hormone in oxidative stress. Thus, in the model of toxic liver damage by carbon tetrachloride (5 ml/kg, i.p.), it was not possible to reveal the antioxidant effects of melatonin (10 mg/kg) on the liver in rats [9]. Also, the ability of melatonin to reduce the activity of LPO processes in the model of toxic liver damage by 2-nitropropane was not confirmed [10]. Melatonin appears to be equally ineffective with respect to the toxic effects of ethanol in the liver. In models of acute and chronic ethanol exposure in rats, melatonin administration did not affect the activity of LPO, glutathione peroxidase, and the level of GSH in the liver [11].

It has been shown that the administration of melatonin at a dose of 10 to 20 mg/kg during the simulation of HIR in rats reduced the activity of ALT and LDH in the blood, the content of α-TNF, the activity of myeloperoxidase and caspases in the liver, liver infiltration with polychromatophilic granulocytes, hepatocellular necrosis and apoptosis [4]. However, it was found that the administration of the pineal gland hormone during HIR to experimental animals contributes to a decrease in NO production in the liver [12]. These data are in conflict with the results of the work, in which it was found that the administration of melatonin to rats during HIR leads to an increase in the level of NO and a decrease in the production of endothelin [13]. Interestingly, both studies used the same melatonin dose, duration of ischemia, and experimental animals. The lack of a clear understanding of the mechanism of action of melatonin in HIR does not yet allow the drug to be used as a therapeutic agent in the clinic. Therefore, the effect of melatonin on NO-dependent processes in hepatic IRI requires additional comprehensive studies.

We found, that melatonin has a pronounced protective effect in the simulation of hepatic IRI in rats. Thus, intraperitoneal administration of this hormone 10 minutes before hepatic ischemia (30 minutes of Pringle maneuver) at dose 10 mg/kg leads to decrease in plasma ALT activity by 75.8% ($p < 0.001$), AST by 75.4% ($p < 0.001$), conjugated dienes by 52.9% ($p < 0.001$), Schiff bases by 53.7% ($p < 0.001$), increase in the content of α-tocopherol by 12.0% ($p < 0.01$), retinol by 30.0% ($p < 0.001$), nitrite/nitrate level by 111.4% ($p < 0.01$) in mixed venous blood on the 120 minutes of reperfusion in relation to animals in which IRI was modulated without the drug. The results of the study of the effect of melatonin in IRI allow us to conclude that this indolamine has a protective effect both on the parameters of the antioxidant system and the degree of oxidative damage to hepatocytes, as well as on the parameters of NO-synthase function of the body. The protective effect of melatonin may be associated with its direct antioxidant properties when interacting with ROS, as well as the ability to enhance the expression of a number of antioxidant enzymes (SOD, GPx, GRd, etc.) [7].

It is known that this hormone can directly interact with the HO*-, forming 3-hydroxylmelatonin, which is then excreted in the urine [14]. In addition, melatonin can interact with H_2O_2 and other ROS, eliminating the latter in the so-called "melatonin antioxidant cascade" [4]. It was found that this indolamine inhibits the expression of iNOS and TNF-α, and also increases the activity of endothelial NO synthase (eNOS) during ischemia-reperfusion [8,15]. Moreover, during reperfusion of organs, melatonin improves the functioning of mitochondria, reducing their generation of ROS and increasing ATP production [16]. This can prevent formation of peroxynitrite - powerful tissue oxidant. In our investigation of the protective mechanisms of melatonin in hepatic IRI with NOS inhibition by L-NAME it was found reducing of protective effect of hormone in rats, allows us to conclude that its protective mechanism is largely bind with gasotransmitter NO [1].

Conclusion

Melatonin has strong and complicative mechanism of protection during hepatic ischemia-reperfusion syndrome, including inhibition of ROS generation and lipid peroxidation, suppression of proinflammatory (NF-kB) and proapoptotic factors. At the same time, melatonin improves SOD and glutathione peroxidase activity, mitochondrial function and can maintain the prooxidant-antioxidant balance and correct biochemical markers of hepatocyte damage (ALT and AST) in this pathology.

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