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Mini Review

Melatonin as an Adjuvant Treatment of Non-Alcoholic Steatohepatitis

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Abstract

Melatonin (N-acetyl-5-methoxytryptamine) is an indoleamine produced by the pineal gland, ovary, testes, bone marrow, gut, placenta, and liver in mammals. However, the indoleamine is also observed in other vertebrate animals, in non-vertebrates animals (insects, crustaceans, planarians), in roots, shoots, leaves, fruits and seeds of vascular plants, and microalgae. Melatonin is both a biological rhythm regulator and an important component of the antioxidant defense system because of its capacity to prevent oxidative stress both a direct (as a free radical scavenger of Reactive Oxygen Species (ROS) and Reactive Nitrogen Species (RNS) and indirect activity stimulating the immune response (modulating the activity of several enzymes including Superoxide Dismutase (SOD), Glutathione Peroxidase (GPx), Glutathione Reductase (GRd), Catalase (CAT), and Nitric Oxide Synthase (NOS), and increasing the effectiveness of other antioxidants like glutathione (GSH).

Because melatonin is produced by the organism, several studies have investigated its capacity to prevent several diseases, including steatohepatitis. Macro vesicular and micro vesicular steatosis are disturbs which occurs during the process of this disease, and it is observed that oxidative stress plays a pivotal role on these processes. The first one is the result of an increased mobilization and availability of Free Fatty Acids (FFAs), elevated hepatic synthesis of FFAs and their esterification into Triglyceride (TG). Reduced export of triglycerides from the liver may also be involved. On the other hand, micro vesicular steatosis is associated with impaired mitochondrial β-oxidation.

Animal studies observed that melatonin may prevent the progression of this disease modulating lipid peroxidation, with improvement of serum transaminases and lipidemic level markers. In humans, recent studies observed similar results. Because of that, the melatonin may play an important role as an adjuvant treatment against non-alcoholic steatohepatitis disease.

The purpose of this review is to know the protective actions of melatonin against molecular hepatic damage produced during Non-Alcoholic Steatohepatitis (NASH) process.

Keywords: Non-alcoholic steatohepatitis; Liver; Melatonin

Melatonin

Physiology and activity

Melatonin (N-acetyl-5-methoxytryptamine) is an indoleamine produced by the pineal gland as well as by many other organs including ovary, testes, bone marrow, gut, placenta, and liver [1-5]. It is synthesized from the essential amino acid L-tryptophan in a process mediated by the action of four enzymes: tryptophan hydroxylase, L-aromatic amino acid decarboxylase, N-acetyl transferase and acetyl serotonin methyl transferase [6]. The regulation of melatonin by light is well-characterized. In humans and other mammals, a peak of melatonin secretion occurs near the middle of the night and then levels begin to drop hours before morning light exposure [7]. Hence, melatonin is known to be an important biological rhythm regulator, but several studies observed that it also plays a pivotal role in the antioxidant defense system [4,5,8-11].

The antioxidant capacity of melatonin is based on its direct action as a free radical scavenger and indirect as a stimulator of cellular antioxidant defense system. Melatonin is observed to generate a scavenger activity that prevents the damage produced because of the activity of Reactive Oxygen Species (ROS) (i.e. superoxide (O_2), Hydrogen Peroxide (H_2O_2), and the Hydroxyl Radical (OH), and Reactive Nitrogen Species (RNS) (nitric oxide (NO) and peroxynitrite ($ONOO^-$) [12]. ROS are generated during normal intracellular metabolism, especially in mitochondria and peroxisomes, and by a variety of cytosolic enzyme systems including NADPH oxidase and cytochrome P_{450} [13]. High concentrations of these substances induce apoptosis (a programmed form of cell death) and cell death (as a result of apoptosis or necrosis) through a process that involves Lipid Peroxidation (LPO), which causes cell edema resulting from 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 caspases. Malondialdehyde (MDA) and 4-hydroxynoneal (4-HNE) are some

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of the major products of LPO [14]. Studies observed that melatonin prevents peroxidation of lipids, preserves membrane physiology and limits the consequential metabolic abnormalities [15].

The indirect means of melatonin to reduce oxidative damage are through stimulation of 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 to H_2O_2), Glutathione Peroxidase (GPx, which reduces H_2O_2 to water), and Glutathione Reductase (GRd, which catalyzes the reduction of glutathione disulfide (GSSG) to the sulfhydryl form glutathione), and promoting the synthesis of another important intracellular antioxidant; glutathione (GSH). Catalase (CAT) activity is also stimulated by the melatonin causing a direct breakdown of H_2O_2 to O_2 and H2O [15,16]. Moreover, melatonin inhibits Inducible Nitric Oxide Synthase (iNOS) and increases Endothelial Nitric Oxide Synthase (eNOS) mRNA levels (regulated by calcium concentration via calmodulin interaction), which are involved in NO^- and $ONOO^-$ generation as a result of its capacity to stimulate or reduce levels of RNS, respectively [17-19].

Finally, it is well known that an innate immune response takes place during LPO leading to an increase in the 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 observed to modulate this effect thereby reducing the NF-kB activation [20-23].

Herein, we summarize in a mini-review the protective actions of melatonin against molecular hepatic damage in NASH subjects.

Melatonin and Non-Alcoholic Steatohepatitis

Non-Alcoholic Fatty Liver Disease (NAFLD) is a common chronic hepatic pathology with an estimated prevalence at one-third of the population in developed countries [24,25]. NAFLD, which is associated with insulin resistance and metabolic syndrome, involves a clinical spectrum which includes simple hepatic steatosis, Non-Alcoholic Steatohepatitis (NASH) and cirrhosis [26,27]. Its prevalence does not differ between sexes and it is also observed that a steatotic liver is not exclusively a problem of the obese population [28]. NAFLD disease is characterized by macro vesicular and micro vesicular steatosis. The first one may be a result of an increased mobilization and availability of Free Fatty Acids (FFAs), elevated hepatic synthesis of FFAs and their esterification into triglyceride (TG). Accumulation of triglycerides in the liver may also be involved. On the other hand, micro vesicular steatosis is associated with impaired mitochondrial β-oxidation. In addition, lipid peroxidation is observed to be related with fat deposition in the liver and its degree increases with the severity of steatosis [29].

Day [30] created the "two-hit model" to explain the steatohepatitic pathogenesis. The "first-hit" is caused by the excess of FFAs in liver (which is produced as a result of insulin resistance, a feature of obesity, type 2 diabetes, hyperlipidemia and metabolic syndrome X). FFAs are esterified to TG making the liver vulnerable to the injury of the "second-hit", which consists of the LPO process with the subsequent generation of ROS, MDA and 4-HNE which induces cell death [31]. In the "second-hit", cytokines are also involved to mediate hepatocyte death/apoptosis (as a result of TNF-α action), and neutrophil chemotaxis (caused by IL-8 action). Resulting from the theory that oxidative stress process may play a role in the hepatic steatosis progression to NASH, melatonin should be effective in reducing its complications through its capacity to modulate it by its direct and indirect actions [32-33].

Animal studies with NAFLD rats observed a strong tendency of melatonin to attenuate liver steatosis and to curtail the rise of liver weight, portal vein pressure, and serum amino transferases [34]. Melatonin was provided in diet (diet plus 5 and 10 mg/kg melatonin for 4 and 8 weeks), and the indoleamine was observed to reduce LPO and oxidative stress damage due to its direct and indirect actions. It was because an increase of reduced GSH levels and the improvement of serum lipidemic level markers [TG, High Density Lipoprotein cholesterol (HDL) and Low Density Cholesterol (LDL)]. However, the authors observed that these benefits were increased in initial phases of liver steatosis compared to later phases, where the reverse or reduction of the severity of steatosis process failed. These modifications were not statistically significant, but this trend is agreed with previous studies [35-36].

Recent studies in rats using tunicamycin (a hepatic steatosis inductor), observed that melatonin (50 mg/kg i.p. for 2 days after the administration of tunicamycin) generated a protective effect against oxidative stress by decreasing TNF-α and F4/80 (a macrophage marker) levels, that were induced by the drug [38]. In addition, the indoleamine influenced micro RNAs (miRNA), which play a pivotal role regulating cellular and metabolic functions. This is important because the over expression of miR-23a increased Ca^{2+} concentration, which causes cell edema, while melatonin controlled the miR-23a responses [37-39]. Similar results were observed with other agents or processes which generate liver steatosis including carbon tetrachloride [40,41] or Lipo Polysaccharide (LPS) toxicities [42].

While in animals there are several studies about melatonin benefits preventing NASH, in human there are few evidence that support this effect. A study developed in 74 patients with NAFLD observed that after a 14-month therapy with melatonin (2x5 mg/day administered orally), or its precursor tryptophan (2x500 mg/day administered orally), plasma levels of gamma-glutamyl transferase (GGT), TG and LDL cholesterol were decreased. These differences were not statiscally significant, while cytokines such as IL-1, IL-6 and TNF-α levels were not decreased. The authors also observed that melatonin and tryptophan reduced inflammation in liver tissue of patients with NASH who underwent a liver biopsy [43]. However, in shorter-term studies in humans, melatonin produced statistically significant differences in ALT and AST levels [44], and cytokines and TNF-α levels [45]. Attending to the result of these studies, more evidence is needed to confirm that melatonin may play a role as a co adjuvant treatment of NASH. It could be interesting because of melatonin is observed to ameliorate liver toxicity caused by chemotherapeutics [46]. In addition, it was not found toxicity in the chronic administration of melatonin in adults up to 1,000 mg daily [47]. Drowsiness is the only consistent side effect of high doses [48].

In conclusion, fatty liver disease is a common illness in developed countries due to the alterations produced recently in the diet because of the changes of life. Several treatments and lifestyle modifications have been developed to improve the prognosis of this disease. Oxidative stress play a pivotal role during this process and,

because of that, melatonin may be an adjuvant treatment due to its antioxidant properties. While in animals there are several studies about melatonin benefits preventing NASH through its direct and indirect actions modulating oxidative stress, few evidence is observed in humans, especially in long-term administration. Because of that, and assuming that melatonin may be administered without toxicity, including chronic administration in a high-dose manner, more studies are needed to clarify the efficacy of melatonin as a co adjuvant treatment of NASH.

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