Melatonin's role preventing steatohepatitis and improving liver transplantation results

Melatonin (N-acetyl-5-methoxytryptamine) is produced by the pineal gland as well as by many other organs including ovary, testes, bone marrow, gut, placenta, and liver. This molecule is both a biological rhythm regulator and an important component of the antioxidant defense system due to its capacity to prevent oxidative stress both a direct and indirect activity stimulating the immune response.

Because melatonin does not produce toxicity due to it is produced by the organism, several studies have investigated its capacity to prevent several diseases, including steatohepatitis and graft rejection in organ transplantation.

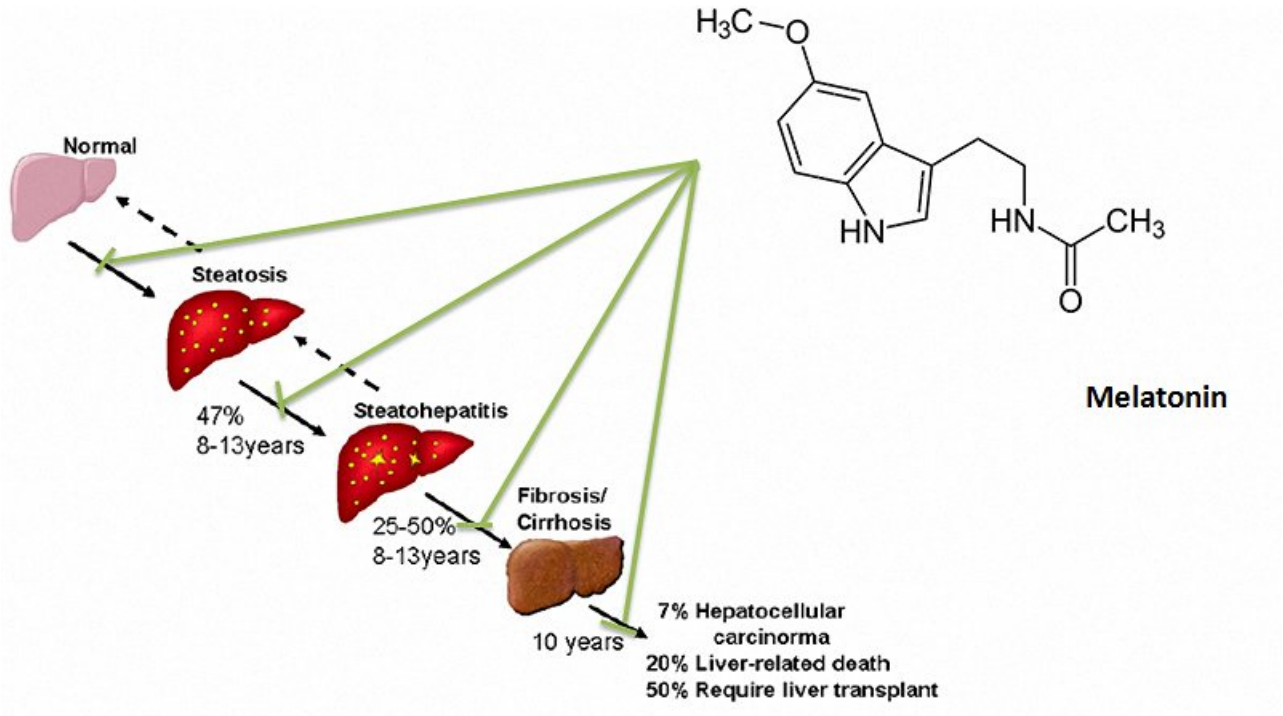

Fig. 1. Melatonin prevents the progression of liver disease due to its antioxidant properties. Steatosis and steatohepatitis may be resolved while fibrosis/cirrhosis and the latest stages of this process not.

Non-alcoholic fatty liver disease (NAFLD) is a common chronic hepatic pathology. Its prevalence in developed countries is estimated at one-third of the population. The clinical spectrum of NAFLD involves simple hepatic steatosis, non-alcoholic steatohepatitis (NASH) and cirrhosis (Fig. 1). NASH is characterized by macrovesicular steatosis, and it 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). When this process is established, the liver is vulnerable to the damage of free radical, which generates oxidative stress and induces cell death.

Several studies in animals observed melatonin benefits preventing steatohepatitis. In human studies with patients affected of NAFLD, melatonin and its precursor tryptophan documented decreased plasma levels of transaminases (ALT and AST), and cytokines (proteins included in the innate immune response). Furthermore, these workers observed that melatonin and tryptophan reduced inflammation in liver tissue in patients with NASH who underwent a liver biopsy.

Alcohol may be involved in liver disease process. Several studies observed increased levels of free radicals and reduced levels of enzymes involved in the innate immune response in patients affected of alcoholic liver disease (ALD). The progression of alcoholic liver damage is well known to cause hepatocellular injury, as well as fibrosis and carcinogenesis. Free radicals and markers of oxidative stress are involved in this process. Due to that, melatonin has been also studied by several authors with encouraging results. In addition to the benefits cited in patients affected of NAFLD, the molecule produced by the pineal gland is observed to prevent the mitochondrial DNA damage in liver as well as other organs brain, heart, or skeletal muscle.

Fibrosis and carcinogenesis are the last stages of liver disease if the medical treatment and lifestyle modifications have not prevented the progression. In this process, melatonin is also observed to improve the results of this treatment reducing the graft rejection ratio due to its capacity to prevent oxidative stress. All the organ transplantation surgeries are based on a process of ischemia-reperfusion. At first time, the liver of the donor suffers a cold ischemia in an organ preservation fluid which prevents the damage to the organ. After that, the liver is implanted in the human and the reperfusion of it is established. Melatonin is observed to reduce graft rejection if it is added to the usual organ preservation fluids. However, during the reperfusion process, the liver suffers an important damage due to the increasing of oxidative stress and free radicals generation. It is in this process where melatonin plays a pivotal role because of its antioxidant properties previously mentioned.

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, including the results of organ transplantation. Oxidative stress play a pivotal role during this process and, because of that, melatonin may be a coadjutant treatment due to its antioxidant properties.

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Publication

Melatonin role preventing steatohepatitis and improving liver transplantation results.
Esteban-Zubero E, García-Gi FA, López-Pingarrón L, Alatorre-Jiménez MA, Ramírez JM, Tan DX, García JJ, Reiter RJ
Cell Mol Life Sci. 2016 Aug