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EFFECTS OF MELATONIN ON AUTOPHAGIC PROCESSES IN THE LIVER OF DIABETIC RATS

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Autophagy is a cellular process that involves lysosomal degradation and recycling of intracellular organelles and proteins. By removing damaged and dysfunctional cellular components in order to maintain energy homeostasis during cellular stress, autophagy can serve as a cytoprotective mechanism. Also, it could lead to cell death if it"s overactive or defective. Molecular mechanisms responsible for the two faces of autophagy are still partially known. Therefore, for the development of therapy based on autophagy modulation, it"s necessary to fully define these processes. This study investigated the role of oxidative stress on autophagic processes in the liver of diabetic rats and effects of melatonin, as an antioxidant, on autophagy initiation/modulation. The liver, as one of the main target organs of insulin, takes an important role in regulation of glucose homeostasis. In diabetes, hypoinsulinemia followed by hyperglycemia increases mitochondrial proton gradient within the cells. In this state organelles become the source of reactive oxidative species leading to macromolecule damage which may cause necrotic, apoptotic or autophagic cell death. In the liver of diabetic rats obtained four weeks after diabetes induction with streptozotocin (65 mg/kg, i.p.), light and electron transmission microscopy showed significant changes in the structure of the cells and a large number of necrotic cells. By using Western blot, immunoprecipitation and confocal microscopy analyses, autophagy in diabetic liver was confirmed by increased expression of proteins required for autophagosome formation, LC3B and Beclin1, and by the presence of Beclin1 interactions with its activator HMGB1. In the state of oxidative stress HMGB1 is relocated from the nucleus to the cytoplasm. Continuous melatonin treatment of diabetic rats (2mg/kg/daily, i.p.) leads to significant reduction of liver damage, presumably through elevated mitochondrial autophagy. Melatonin additionally contributes to elevated expression of LC3B and Beclin1, HMGB1-Beclin1 interactions and autophagosome formation. Thus, it seems that melatonin protects the liver from diabetes induced damage by favoring autophagy as a protective mechanism.