Long-term melatonin administration improves glucose homeostasis and insulin resistance state in high-fat-diet fed rats

Research Article

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Abstract: Emerging evidence support an important role of reactive oxygen species in various forms of insulin resistance. It is identified that melatonin has antioxidant properties and prevents toxic effects of reactive oxygen species. In this study, we sought to assess the involvement of melatonin in the progression of insulin resistance in response to a high-fat diet (HFD) and to investigate the underlying mechanisms. Male rats were fed with a control diet, a high-fat diet, or a high-fat diet supplemented with melatonin (5 mg kg^{-1}, i.p.) for 10 weeks. Glucose homeostasis, insulin sensitivity, antioxidative potency, and metabolic profiles in the rats were evaluated. Our results showed that a HFD led to increasing body mass, adipose tissue weight, plasma insulin, total cholesterol (TC), triglycerides (TG), free fatty acids (FFA), and decreased HDL-cholesterol (HDL-C) in rats. There was also a significant increase in the level of malondialdehyde (MDA) and decrease in superoxide dismutase (SOD) activity, oxidative stress markers both in the plasma and liver. An enhanced hepatic phosphoenolpyruvate carboxy-kinase (PEPCK) activity and RNA expression were observed. Impaired insulin signaling was evidenced by reducing insulin receptor substrate 2 (IRS2) tyrosine phosphorylation and protein kinase B (PKB) serine phosphorylation in response to insulin. Overactivation of stress-activated protein kinases JNK was also observed in the liver of HFD rats. However, simultaneous administration of melatonin to HFD rats significantly reduced oxidative stress in the system and liver, markedly improved impaired glucose homeostasis, insulin sensitivity, antioxidative potency, metabolic profiles and all the aforesaid adverse changes in HFD rats. Our results demonstrated that anti-oxidative property of melatonin is sufficient to ameliorate the insulin resistance condition, leading to the improvement of glucose homeostasis and the restoration of hepatic insulin signaling in a rat model of HFD-induced insulin resistance.

Keywords: Melatonin • Insulin resistance • Oxidative stress

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1. Introduction

Obesity is a common characteristic of type 2 diabetes, and is also a major contributing factor to insulin resistance, a hallmark feature of type 2 diabetes. Insulin resistance, defined as a decreased ability of target tissues and organs such as fat, skeletal muscle and liver to respond normally to insulin, most often precedes the overt diabetes by many years and is the best predictor of whether or not an individual will become diabetic [1,2]. Although there are genetic factors that contribute to insulin resistance, insulin resistance is also induced by acquired factors such as obesity, sedentary life style and hormone excess. Consumption of high-calories diets is

considered to be one of the main environmental triggers [3]. Insulin resistance is manifested by decreased insulin-stimulated glucose transport and metabolism in adipocytes/skeletal muscle and by impaired suppression of hepatic glucose production in liver. At the molecular level, insulin resistance correlates with impaired insulin signaling in insulin-sensitive tissues. However, the definite mechanisms responsible for insulin resistance have not yet been elucidated.

Oxidative stress, defined as a serious imbalance between the production of reactive species and antioxidant defenses leading to potential tissue damage, has been implicated in the pathogenisis of insulin resistance [4]. There is considerable evidence that