EFFECTS OF MELATONIN ON MITOCHONDRIAL FUNCTION AND INSULIN RESISTANCE IN RAT SKELETAL MUSCLE

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Metabolic syndrome has been associated with a reduction in nocturnal pineal production of melatonin with aging and an increased risk of coronary diseases, type 2 diabetes mellitus (T2DM) and death. The present study investigated the metabolic pathways involved in the effects of melatonin on mitochondrial function and insulin resistance in rat skeletal muscle. The effect of melatonin was tested both in vitro in isolated rats skeletal muscle cells and in vivo using pinealectomized rats (PNX). Insulin resistance was induced in vitro by treating primary rat skeletal muscle cells with palmitic acid for 24 hr. Insulin-stimulated glucose uptake was reduced by palmitic acid followed by decreased phosphorylation of AKT which was prevented my melatonin. Palmitic acid reduced mitochondrial respiration, genes involved in mitochondrial biogenesis and the levels of tricarboxylic acid cycle intermediates whereas melatonin ounteracted all these parameters in insulinresistant cells. Melatonin treatment increases CAMKII and p-CREB but had no effect on p-AMPK. Silencing of CREB protein by siRNA reduced mitochondrial respiration mimicking the effect of palmitic acid and prevented melatonin-induced increase in p-AKT in palmitic acid-treated cells. PNX rats exhibited mild glucose intolerance, decreased energy expenditure and decreased p-AKT, mitochondrial respiration, and p-CREB and PGC-1 alpha levels in skeletal muscle which were restored by melatonin treatment in PNX rats. In summary, we showed that melatonin could prevent mitochondrial dysfunction and insulin resistance via activation of CREB-PGC-1 alpha pathway. Thus, the present work shows that melatonin play an important role in skeletal muscle mitochondrial function which could explain some of the beneficial effects of melatonin in insulin resistance states.

Key words: diabetes, insulin resistance, melatonin, mitochondrial function, skeletal muscle