Journal of Functional Foods 48 (2018) 167–172

Contents lists available at ScienceDirect

Journal of Functional Foods

journal homepage: www.elsevier.com/locate/jff

Melatonin increases magnesium concentrations in white adipose tissue and pancreas of diabetic obese rats

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ARTICLE INFO

Keywords:
Melatonin
Magnesium
Diabetic obese rats
White adipose tissue and organs

ABSTRACT

Melatonin is a natural bioactive compound, whose intake by obese diabetic Zucker (ZDF) rats improves this pathology. Hypomagnesaemia has also been observed in diabetes, and magnesium (Mg) is known to play an essential role in carbohydrate metabolism. In this study we have determined the effect of melatonin intake on Mg concentrations in white adipose tissues and organs in ZDF rats. This study reveals for the first time that melatonin intake increases Mg concentrations in subcutaneous lumbar, visceral, omentum, and gonadal adipose tissue and in the pancreas. These findings may be related to an improvement in the homeostatic regulation of adipocytokines produced by white adipose tissues, and to a reduction in plasmatic oxidative stress, which would lead to a decrease in insulin resistance and improvement in glucose homeostasis. These results open up the beneficial use of melatonin for the development of functional foods to ameliorate glucose homeostasis in obesity-associated diabetes.

1. Introduction

Melatonin (*N*-acetyl-5-methoxytryptamine) is produced in the pineal gland and in peripheral organs and tissues. The amount of melatonin in tissues (extrapineal) is far in excess of that in the circulation, but only circulating melatonin possesses chronobiotic properties (Acuña-Castroviejo et al., 2014; Hardeland et al., 2011; Ribas-Latre et al., 2015). Although melatonin was initially characterized as a hormone primarily involved in the circadian regulation of physiological and neuroendocrine functions, subsequent studies found that it can counteract free radical damage by various mechanisms of action (Othman, El-Missiry, Amer, & Arafa, 2008; Reiter et al., 2016; Tan et al., 2002; Zhang & Zhang, 2014; ; Escudero-López et al., 2016), supporting a role for this indoleamine against oxidative stress and inflammation. There is also considerable evidence on the beneficial effects of melatonin supplementation against obesity and related comorbidities (Favero et al., 2015; Hussein, Ahmed, Hassan, & Ahmed, 2007; Navarro-Alarcon, Ruiz-Ojeda, Blanca-Herrera, A-Serrano et al., 2014; Prunet-Marcassus et al., 2003; Tan, Manchester, Fuentes-Broto, Paredes, & Reiter, 2011; Wolden-Hanson et al., 2000). In previous studies, we investigated the anti-obesity and antidysmetabolic effect of chronic melatonin administration in ZDF rats, demonstrating that melatonin limits obesity and improves metabolic syndrome (Agil et al., 2011, 2012, 2013) in part through via browning of subcutaneous white adipose tissue (WAT; Jimenéz-Aranda et al., 2013). Moreover, recently we reported that melatonin increased their interscapular brown adipose tissue (BAT) amounts and their mitochondrial mass and function probably by inducing proliferation and at the same time promotes differentiation of pre-adipocytes into thermogenic adipocytes (Fernández-Vázquez, Reiter, & Agil, 2018). In this line, our group previously reported that chronic oral melatonin administration improved glucose homeostasis in young Zucker Diabetic Fatty (ZDF) rats, by intensifying β-cell function and insulin action (Agil et al., 2012) and had a positive effect on dyslipidemia, the pro-inflammatory state, and oxidative stress, which underlie development of the metabolic syndrome (Agil et al., 2011, 2013; Fernández-Vázquez et al., 2018). Furthermore, pinealectomy has been related to a deficiency in insulin signaling pathways and a reduction in GLUT4 gene expression, inducing insulin resistance and glucose intolerance (Zanquetta, Seraphim, Sumida, Cipolla-Nieto, & Machado, 2003).

Agil et al. (2012) previously verified that melatonin supplementation improved glucose homeostasis in ZDF rats, reducing fasting insulinemia, the HOMA-IR insulin resistance index, and blood leptin levels, and increasing adiponectin blood levels. Given that leptin and

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https://doi.org/10.1016/j.jff.2018.07.018
Received 4 May 2018; Received in revised form 13 June 2018; Accepted 2 July 2018
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adiponectin are synthetized by WATs, melatonin administration would significantly affect their homeostasis and functioning, reducing leptin resistance and thereby producing a decrease in blood leptin levels and an increase in satiety. This would facilitate weight reduction in melatonin-treated ZDF rats in comparison to controls (Agil et al., 2011). Melatonin supplementation increased blood adiponectin concentrations, reducing the insulin resistance of ZDF rats and improving their glucose homeostasis (Agil et al., 2012).

Type 2 diabetes mellitus has frequently been associated with hypomagnesemia (Gommers, Hoenderop, Bindels, & De Baaij, 2016; Guerrero-Romero, Rascón-Pacheco, Rodríguez-Morán, Escobedo de la Peña, & Wacher, 2008; Rodríguez-Morán & Guerrero-Romero, 2011; Sales & Pedrosa, 2006; Simmons, Joshi, & Shaw, 2010) which has been reported in 14–48% of diabetic patients *versus* 2.5–15% of healthy controls (Pham, Pham, Pham, Miller, & Pham, 2007). In a recent cross-sectional study, hypomagnesemia was associated with an increased risk of complications, including cardiovascular disease (Kunutsor, Khan, & Laukkanen, 2016). In animal studies, plasma magnesium (Mg^{2+}) concentrations were found to be lower in ZDF rats than in their lean littermates (ZL rats; Navarro-Alarcon, Ruiz-Ojeda, Blanca-Herrera, Kaki et al., 2014). Importantly, Mg^{2+} supplementation has been reported to have beneficial effects on insulin sensitivity and metabolic control, suggesting that Mg^{2+} may be a key factor in the etiology and management of diabetes (Dong, Xun, He, & Qin, 2011; Guerrero-Romero & Rodriguez-Morán, 2014; Guerrero-Romero, Simental-Mendía, Hernández-Ronquillo, & Rodriguez-Morán, 2015; Rodriguez-Moran & Guerrero-Romero, 2003; Veronese et al., 2016).

With this background, we hypothesized that melatonin supplementation would regulate Mg^{2+} concentrations at cellular level in different tissues and thereby contribute to improving Mg^{2+} homeostasis in diabetes. Therefore, the objective of this study was to evaluate the effects of melatonin administration on Mg^{2+} homeostasis in muscle, brain, liver, pancreas, and gonadal, visceral, renal, omental, and subcutaneous lumbar adipose tissue in young male ZDF and ZL rats.

2. Material and methods

2.1. Animals and experimental protocols

Five-week-old male ZDF rats (fa/fa; 180–200 g body weight [BW]; $n = 20$) and male lean littermates (ZL, fa/-; 120–140 g BW; $n = 20$) from Charles River (Barcelona, Spain) were kept on Purina 5008 rat chow (23% protein, 6.5% fat, 58.5% carbohydrates, 4% fiber, 6.8% ash) and tap water *ad libitum*. Animals were housed 3/4 per clear plastic cage in a controlled room with a 12 h dark–light cycle (lights on at 07:00 h). The study complied with European Union guidelines for animal care and protection and was approved by the Ethics Committee of the University of Granada (Granada, Spain). At the age of 6 weeks, ZDF and ZL rat groups were each subdivided into two groups ($n = 10$): control groups (ZDF-C and ZL-C) that received no treatment; and melatonin-treated groups (ZDF-M and ZL-M). A vehicle group was not included, as previous research found no significant differences between untreated and vehicle-treated groups (Agil et al., 2015). Melatonin was dissolved in a minimum volume of absolute ethanol and diluted to a final solution of 0.066% (w/v) in the drinking water, providing treated animals with a daily dose of 10 mg/kg BW. Fresh melatonin and vehicle solutions were prepared twice a week, adjusting the melatonin dose to the body weight. Water bottles were protected from light by an aluminum foil cover. After 6 weeks of treatment and overnight fasting, animals were anesthetized with sodium thiobarbital (thiopental) and killed between 09:00 and 11:00 h.

Subcutaneous lumbar and visceral WAT samples (*peri*-renal, gonadal, and omentum adipose tissues) and samples from other tissues (liver, muscle, pancreas, brain) were obtained by surgical extirpation, washed in saline solution, and kept at −80 °C until analysis (Agil et al., 2015).

2.2. Equipment and reagents

Mg^{2+} concentrations were measured using a 1100 B Atomic Absorption Spectrometer equipped with a Ca^{2+} and Mg^{2+} multi-element hollow cathode lamp (Perkin-Elmer, Germany). Reagent grade water was obtained using the R015 Milli-Q system (Waters, Medford, MA), and tissue samples were mineralized in a Multiplaces Selecta mineralization block (Barcelona, Spain; Agil et al., 2015).

Melatonin was purchased from Sigma Chemicals (Madrid, Spain). A standard solution of Mg^{2+} (1000 mg/L; Tritisol, Merck, Darmstadt, Germany) was used to prepare calibration graphs. Analytical grade reagents were used to prepare all solutions: HNO_3 (65%) and HClO4 (65%) (Suprapur, Merck). Standards for calibration and dilutions were prepared immediately before use using deionized water with a specific resistivity of 18 mΩ cm (Millipore, Waters, Mildford, MA).

2.3. Magnesium determination by flame atomic absorption spectrometry (AAS)

Tissue samples (from subcutaneous lumbar, *peri*-renal, gonadal, or omentum adipose tissue, liver, muscle, pancreas, or brain) of 0.100–0.200 g were weighed in a Pyrex glass tube and 0.8 mL HNO_3 was added, followed by heating for 15 min at 80 °C, transfer to a multistage mineralization block (Multiplazas Selecta; Barcelona, Spain), and subsequent heating for 45 min at 180 °C. Next, 0.8 mL HNO_3:$HClO_4$ (4:1) was added, and the mixture was then heated at 200 °C for a further 90 min. The solution obtained was diluted to 2.5 mL with milli-Q water, and Mg^{2+} concentrations were determined by direct aspiration in the flame of the atomic absorption spectrophotometer using a previously optimized linear calibration method (Gámez et al., 1997). The mean Mg^{2+} concentration of 2.11 ± 0.07 mg/dL obtained for the reference material (CRM Human Serum Chengdu Shuyang Medition Factory, Chengdu, China; National Research Center for CRM'1, Beijing, China, United Analysis and Measurement Center of Sichnan, Chengdu, China) did not significantly differ ($p > 0.05$) from the certified value of 2.04 ± 0.08 mg/dL.

2.4. Statistical analysis

SPSS 15.0 for Windows (IBM, Chicago, IL) was used for statistical analyses. Results are expressed as the arithmetic mean and the standard error of the mean (SEM). Normal distribution was checked with the Kolmogorov–Smirnov test and the homogeneity of variance with Levene's test. Parametric variables were compared using two-way ANOVA and Bonferroni's multiple comparisons test, considering $p < 0.05$ as statistically significant. Non-parametric variables were compared using the Kruskall-Wallis test, considering $p < 0.05$ as statistically significant.

3. Results and discussion

Fig. 1A depicts the Mg^{2+} concentrations measured in white adipose tissue (WAT) samples of subcutaneous lumbar and visceral adipose tissue (*peri*-renal, gonadal, and omentum adipose tissues) from young male ZDF rats and their lean littermates (ZL); Fig. 1B exhibits the concentrations found in liver, muscle, pancreas, and brain samples. Mg^{2+} concentrations did not significantly differ between ZDF-C and ZL-C rats, indicating that concentrations in these tissues are not significantly influenced by the presence of diabetes. In ZDF rats, melatonin treatment significantly increased Mg^{2+} concentrations in subcutaneous lumbar, *peri*-renal, gonadal, and omentum adipose tissue (Fig. 1A) and in the pancreas (Fig. 1B; $p < 0.05$). Mean omentum Mg^{2+} concentrations were significantly higher in ZDF-M rats than in ZL-M and ZL-C animals ($p < 0.05$), but no significant differences were found between ZDF-M and ZDF-C rats in liver, muscle, or brain Mg^{2+} concentrations (Fig. 1B; $p > 0.05$). According to these findings, neither obesity nor

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