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Magnesium and Melatonin Co-Administration Attenuates Blood Glucose Levels in Streptozotocin-Induced Diabetic Rats

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Abstract

Diabetes mellitus (DM) is a serious metabolic disorder characterized by elevated blood glucose. The raised blood glucose level if not properly managed can results in damage and failure of several vital organs such as the eyes, kidneys, nerves, heart, and blood vessels. The aim of this study was to evaluate the effects of co-administration of melatonin and magnesium on blood glucose level of streptozotocin-induced Type 1 diabetic Wistar rats. To achieve this aim sixty-four Wistar rats were used in the study. Streptozotocin (STZ) was used to induce chemical type 1 diabetes mellitus (T1DM) after two weeks acclimatization period in fifty-eight Wistar rats. Fifty-three rats were diabetic and fourty-eight diabetic rats were randomly distributed in eight groups and six normal normoglycaemic rats were used as control. The animals were assigned into nine groups as follows, Normal control group (NC), Diabetic control (DC) group, Melatonin Low dose group of 10 mg/kgb (MLD), magnesium low dose group of 240 mg/kgbw (MgLD), melatonin and magnesium combined low dose group of 10mg/kgbw+240mg/kgbw (MMgLD), melatonin high dose group of 20mg/kgbw (MHD), magnesium high dose group of 480mg/kgbw (MgHD), melatonin and magnesium high dose combined group of 20mg/kgbw+480mg/kgbw (MMgHD) and insulin at 500mg/kgbw group (IN). Melatonin and insulin were administered through intraperitoneal injections (IP) while magnesium was by oral administration. The control groups were given placebo and all group treatment was for twenty-one days. Blood glucose was measured weekly in all groups by day 8, day 15 and day 22. At the end of the evaluation Day 22, the blood glucose levels showed a highly significant decrease ($p<0.05$) in melatonin treatment group at low dose (MLD), melatonin and magnesium combined group at low doses (MMgLD), melatonin treatment group at high doses (MHD) and insulin treated group (IN) when compared with normoglycaemic group (NC) while groups treated with Magnesium at low doses (MgLD), magnesium treated group at high doses and melatonin and magnesium treatment group at high doses (MMgHD) showed no significant decrease ($p<0.05$) in blood glucose levels as compared with diabetic control (DC). Melatonin and magnesium co-administration has hypoglycaemic effects on blood glucose levels in STZ-induced type 1 diabetic Wistar rats.

Keywords: Diabetes, Hyperglycaemia, Hypoglycaemia, Magnesium, Melatonin, Typ1 Diabetes.

1.0 INTRODUCTION

The incidence of people in the world with diabetes has increased dramatically over recent years. Reports released by the World Health Organization in the year 2016 states that more than 400 million people live with diabetes [1, 2]. This incidence may rise to 591.9 million in 2035. The reports further states that there is an expected increase in the number of adults with diabetes in low-income countries to about 108%, lower middle-income countries by 60%, upper middle-income countries to 51%, and high-income countries to 28% [3]. Type 1 diabetes and type 2 diabetes are heterogeneous diseases in which clinical presentation and disease progression may differ considerably. The need to classify this disease is important for determining therapy, but several individuals cannot be grouped as having type 1 or type 2 diabetes at the onset of diagnosis.

The established notion that type 2 diabetes mellitus occurs only in adults and that type 1 diabetes

only in children are no longer accurate, as both diseases occur in both age-groups. Children with type 1 diabetes typically present with the hallmark symptoms of polyuria/polydipsia, and approximately one-third present with diabetic ketoacidosis (DKA) [4].

The onset of type 1 diabetes may be more variable in adults, and they may not present with the classic symptoms seen in children. Occasionally, patients with type 2 diabetes may present with DKA, particularly ethnic minorities [5].

In both type 1 and type 2 diabetes, various genetic and environmental factors can result in the progressive loss of β-cell mass and/or function that manifests clinically as hyperglycemia. Once hyperglycemia occurs, patients with all forms of diabetes are at risk for developing the same chronic complications, although rates of progression may differ. The identification of individualized therapies for diabetes in the future will require better characterization of the many paths to β-cell demise or dysfunction [6].

Various hypoglycaemic drugs, such as sulfonylurea, metformin is being used for the treatment of diabetes but their use is restricted by their limited action and accompanying side effects such as hypoglycaemic shock and weight gain. Insulin treatment also fails to prevent the long-term complication. Conventional measures used in the management of diabetes usually aim at improving glucose homeostasis and delay the onset of complications but, these measures are not curative [7]. Previously some researchers have shown that weight gain, drug resistance to Insulin and hypoglycaemia are some common side effects associated with conventional treatment to hyperglycaemia associated diabetes mellitus.

Many complications of diabetes result due to an increased free radical load [8]. The search for natural antioxidative agents that will ameliorate the harmful effects associated with hyperglycaemia still continues in spite of considerable progress in the management of diabetes mellitus by synthetic drugs. There has been significant gain to achieve the above objectives with many antioxidants hence the need to combine melatonin and magnesium at varied doses to assess their hypoglycaemic effects and to eliminate or minimize the harmful effects associated with conventional drugs.

II. MATERIALS AND METHODS

2.1 Materials

The following materials were used in the study, Elevated Plus Maze (EPM) study chamber, Plastic Cages, Spectrophotometer auto analyzer, blood sample containers, organ sample containers, Centrifuge, Temperature controlled refrigerator, Microwave oven, water bath, humidity chamber, Leica Auto processor, Leica Auto stainer, Leica DM750, Camera ICC50 E, AmScope D200 digital camera, MRC spectrophotometer.

2.2 Bioactive compounds and drugs used in the study were

Melatonin M5250-1G (Sigma Aldrich USA), Magnesium (Randox, USA) Streptozotocin SP0130 (Sigma Aldrich, USA),

2.3 Source of animals and management

Sixty-four Male Wistar rats weighing of 120–150 g were purchased from the Faculty of Pharmaceutical Sciences Animal House of the Ahmadu Bello University, Zaria and selected for the study. The rats were maintained on a day and night cycle at room temperatures and have *ad libitum* access to food (Standard feeds, standard rat pellets) and water. All experiments were performed between 08:00 and 12 hours.3.4 Methodology.

2.4. Induction of Type 1 Diabetes Mellitus

Type 1 diabetes mellitus (T1DM) was induced after 2 weeks acclimatization period, a baseline blood glucose levels and behavioral and cognitive assessment were performed for all test animals. This was done to ensure that the animals were all normoglycaemic and that they all exhibit normal cognitive function to remove bias using the elevated plus maze (EPM). Fifty-Eight male Wistar rats were randomly selected and given a single dose of intra peritoneal injection of streptozotocin, (STZ) (Sigma, Aldrich, USA), at 55mg/kg body weight in citrate buffer (0.1M, pH 4.5). The solution (STZ in citrate buffer) was used within 5 minutes to induce chemical diabetes in the Wistar rats after an overnight fast for twelve hours.

3.4.1 Hyper glycaemia screening and confirmation of T1DM

Four days after streptozotocin was used to induced diabetes mellitus, blood was collected from the tail vein following an overnight fast [9, 10]. Fasting blood sugar (FBS) was measured with a standard glucometer (Optimum, Germany). The day that hyperglycaemia above 200mg/dl (11 mmol/l) was confirmed was considered to be diabetic day 1. Rats with fasting blood glucose levels lower than 200 mg/dL (11mmol/L) were excluded from the study.

III. RESULTS AND DISCUSSIONS

3.1 Blood Glucose Levels evaluation

Blood glucose evaluation as shown in Table 4.3 showed the results obtained from Wistar rats (normal and STZ induced diabetic control) and treated groups of Melatonin and Magnesium. At the end of first week of treatment day 8, there was significant ($p<0.05$) reduction of blood glucose levels in melatonin treated group at low dose (10mg/kgbw) (MLD), melatonin and magnesium combined treated group (M MgLD) at low dose each (10mg and 240 mg/kgbw respectively), melatonin treated group (MHD) at high dose

(20mg/kgbw), and insulin treated group (IN) at 1IU as compared with normal control group (NC) while there was reduction of blood glucose levels in Melatonin and magnesium at high doses (MMgHD) but was not significant ($p<0.05$) when compared to control group (NC). There was no significant blood glucose reduction ($p<0.05$) in magnesium treatment group at low dose (MgLD) and magnesium treatment at high dose group alone (MgHD) as compared with diabetic control Group, (DC).

On day 15 the result obtained showed that there was significant blood glucose level decrease ($p<0.05$) in Melatonin treatment group at low dose (MLD), melatonin and magnesium treatment group at low dose (MMgLD), melatonin group at high dose (MHD) and INat 1IU as compared with normoglycaemic group (NC), while there was no significant blood glucose decrease ($p<0.05$) in groups magnesium treatment group at low dose (MgLD), magnesium treatment group at high dose (MgHD) and melatonin and magnesium treatment group at high dose (MMgHD as compared with diabetic hyperglycemic diabetic control (DC).

At the end of the evaluation Day 22, the blood glucose levels showed a highly significant decrease ($p<0.05$) in blood glucose levels in melatonin treatment group at low dose (MLD), melatonin and magnesium combined group at low doses (MMgLD), melatonin treatment group at high doses (MHD) and IN treat at 2IU as compared with normoglycaemic group (NC) while groups treated with Magnesium at low doses (MgLD), magnesium treatED group at high doses and melatonin and magnesium treatment group at high doses (MMgHD) showed no decrease ($p<0.05$) in blood glucose levels as compared with diabetic control (DC).

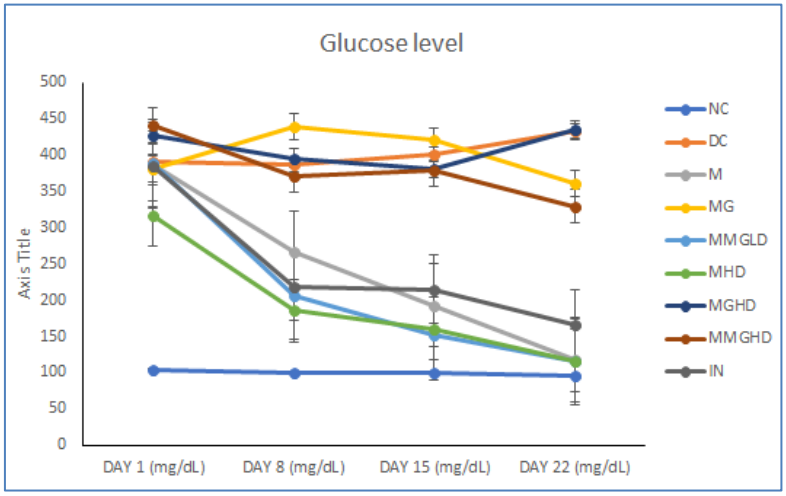

Fig-1: Mean Change in Blood Glucose levels of Melatonin and Magnesium treated STZ induced diabetic Wistar rats.

Values are expressed as mean±SEM. Values with different superscript alphabets in a column are significantly different ($p<0.05$).

KEY: NC (control), DC (Diabetic control), MLD (Melatonin), MgLD (Magnesium), MMgLD (Melatonin and magnesium low dose), MHD (Melatonin high dose), MgHD (Magnesium high dose), MMgHD (Melatonin and Magnesium high dose), IN (Insulin).

In this study values obtained in Fig 1 showed decrease in blood glucose levels was observed in groups administered melatonin at low and high doses and in combined melatonin and magnesium treatment at low doses which showed significantly weekly alteration in blood glucose levels towards the normal control group. There was a significant increase in blood glucose levels in magnesium treatment at low and high doses alone and in combined high doses of melatonin and magnesium treated group in STZ induced diabetes which was significantly high when compared to the diabetic control group. Similar reports [11] showed the hypoglycaemic efficacy of melatonin and that there was a significant weekly alterations of blood glucose levels towards the normal range and that the weekly blood glucose level was significantly higher in STZ induced diabetic rats. Reports published [12] also showed the hypoglycaemic effects of melatonin when administered at 10 mg/kg and that melatonin reduced and normalized STZ induced hyperglycaemia in Wistar rats [11]. These results are similar to reports by [13] whose investigations reported that Mg supplementation in STZ induced diabetic rats also reduces insulin resistance and improves glycaemic control indicators among type 2 diabetic patients. Melatonin on its own has hypoglycaemic effects and it caused a decreased and normalized blood glucose levels in alloxan induced diabetic rats, probably due to its inhibitory effects on catecholamine's by inhibiting ACTH-stimulating cortisol production [14]. Poor intracellular Mg concentration and increased intracellular free calcium as found in type 2 diabetes patients, may cause insulin resistance [15]. In contrast, higher magnesium levels

correspond to a greater degree of insulin sensitivity [16, 17]. We confirmed that magnesium co-administration with melatonin have hypoglycaemic effects on blood glucose levels in STZ-induced diabetic rats and as previously stated that magnesium supplementation in individual with Type 2 diabetes (T2D) is an adjuvant therapy in the prevention and management of diabetes [18]**.**

IV. CONCLUSION

Melatonin administration at low and high doses when co-administered with low dose magnesium has synergistic effects to normalize blood glucose levels in STZ-induced diabetic rats, thereby reversing hyperglycaemic in diabetic Wistar rats.

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