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Oral magnesium reduces gastric mucosa susceptibility to injury in experimental diabetes mellitus

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ABSTRACT

This study investigated the effect of magnesium on the gastric defence mechanism in alloxan-diabetic male Wistar rats.

Sixty rats were randomly divided into 2 groups, A (n = 40) and B (n = 20). Each group was subdivided into control, diabetic untreated (DU), diabetic magnesium (250 mg/kg) treated (DMg250) and diabetic insulin (3 IU/kg s.c) treated (DI). Diabetes was induced with alloxan (120 mg/kg) and both groups were treated for 14 days. By day 14, group A rats were sacrificed, the stomach excised and evaluated for histopathology, mucus content, parietal and mucus cell counts. Blood was withdrawn from the orbital sinus of group B rats for biochemical evaluation (blood glucose, superoxide dismutase (SOD), lipid peroxidation (LP) and nitric oxide (NO)) and later sacrificed for gastric SOD, LP and NO evaluation.

Blood glucose level was reduced ($p < 0.05$) in all treatment groups compared to DU. Gastric SOD, parietal and mucus cell counts were increased ($p < 0.05$) in the DMg250 and DI compared to DU. Serum LP and NO were reduced while gastric LP was increased in the DMg250 compared to DU. Gastric NO and mucous content were significantly reduced ($p < 0.05$) in all diabetic groups compared to control. The gastric mucosa of the DU group had haemorrhage, inflammation and parasites embedded. The DMg250 and DI had normal submucus and muscle layers with reduced inflammation.

Oral magnesium treatment in diabetes exerts hypoglycaemic effects, reduces serum nitric oxide and lipid peroxidation, increases gastric superoxide dismutase, mucous cell count and reduces the susceptibility of the gastric mucosa to ulceration.

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1. Introduction

Diabetes mellitus is a metabolic disorder characterized by hyperglycaemia which occurs as a result of defects in insulin secretion, action or both. It is a disorder with long term complication such as diabetic nephropathy, retinopathy, cardiopathy and neuropathy. Studies have shown that patients with long standing diabetes mellitus develop gastrointestinal symptoms such as abdominal pain, diarrhoea, and delayed gastric emptying [1]. Several reports indicate that diabetes mellitus increases the mucosal susceptibility to ulcerogenic stimuli, gastric ulceration, severe acute gastric inflammation and ulcer disease [2–4]. Experimental diabetes has been shown to impair gastric ulcer healing [5–7] and though incidences of gastric ulcer in diabetes may be infrequent, gastric bleeding is often fatal in diabetes [4]. Studies on the pathogenesis of gastric ulcer formation during diabetes are scanty [1]. The increased susceptibility of the gastric mucosa to ulceration in diabetes mellitus could be due to back diffusion of hydrogen ions in the stomach [8], reduction in gastric blood flow and rapid changes in blood glucose level [9]. There are also reports that suggest the role of free radicals and loss of mucosal glycoprotein in the pathogenesis of gastric ulceration in diabetes mellitus [10].

Goel and Sairam [11] classified agents that have gastroprotective properties into two groups; those that decrease or counter acid/pepsin secretion and those that afford cytoprotection by virtue of their effects on mucosal defensive factors (mucin secretion, cellular mucus, antioxidants, bicarbonate secretion, mucosal blood flow and cell turnover). Within the gastric mucosa, a complex system of interacting mediators that contribute to strengthening its resistance against injury has also been reported [12]. Reactive oxygen species (ROS) have been reported to be one of the causative factors for mucosal lesions through oxidative stress. The radicals promote mucosal damage by causing degradation of the epithelial basement components, complete alteration of the cell metabolism and deoxyribonucleic acid (DNA) damage [13]. The gastric mucosa can be protected from the harmful effects of free radical through

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the action of antioxidants that scavenge free radicals and the activities of nitric oxide which include reduced mast cell degranulation, cytokine release, neutrophil adherence and secretion as well as increase mucus secretion and gastric epithelial blood flow [14]. Thus the up-regulation of nitric oxide and antioxidant activities in the gastric mucosa may represent a protective mechanism against the formation of gastric ulceration.

Magnesium, a micronutrient known to function as an essential cofactor for more than 300 enzymatic processes in the body [15,16] has been reported to prevent cardiovascular disease, improve insulin secretion and sensitivity, improve insulin-stimulated glucose uptake and stabilize blood glucose levels in diabetes mellitus [17,18]. It is also known to be an important constituent of antacids and its use for constipation and dyspepsia are accepted as standard care despite limited evidence.

It has been observed that in alloxan diabetic rats, oral magnesium treatment delays the onset of hyperglycemia [19], modulates gastrointestinal motility [20] and possesses both gastro-protective and anti-ulcerogenic effects [21]. In normal animals, its anti-ulcerogenic properties have been ascribed to its ability to decrease parietal cell count and increase mucous cell count [22]. Sandor et al. [23] also suggested that the gastro-protective effect of magnesium could be due to its ability to indirectly reduce gastric acid secretion via inhibition of calcium signalling mechanisms on the parietal cells. However, it is not confirmed whether oral magnesium supplementation potentiates the gastric mucosal defence systems thus reducing its susceptibility to gastric inflammation and ulcer disease in diabetes mellitus. The gastro-protective effects of oral magnesium treatment in alloxan-induced diabetic rats through its effect on serum and gastric antioxidants, lipid peroxidation, nitric oxide levels, gastric histopathology, mucus content, parietal and mucus cell counts were therefore investigated in Wistar rats.

2. Materials and methods

2.1. Animal grouping and experimental protocol

Sixty (60) adult male Wistar rats were housed in standard well aerated laboratory cages and maintained at $27 \pm 3^{\circ}$ with 12-h light–dark cycle. They were fed on standard rat chow and allowed free access to drinking water according to the regulation and ethics regarding use of animals' in the University of Ibadan. The animals were randomly divided into 2 study groups A ($n = 40$) and B ($n = 20$). Each study group was further subdivided into 4 groups as follows: group 1 was control and received orally 0.2 ml distilled water daily for 14 days. Animals in groups 2–4 were made diabetic with a single intraperitoneal administration of alloxan monohydrate (120 mg/kg) and divided as follows: Group 2, diabetic untreated group (DU), group 3 diabetic animals treated with 250 mg/kg magnesium (DMg250) and group 4 diabetic animals treated with 3 IU/kg insulin (DI) for 14 days respectively. Animals with sustained blood glucose of $\geq$200 mg/dl after 5 days were considered as being diabetic [24]. All magnesium treatments were administered orally using an oral cannula while insulin was prepared fresh daily and administered subcutaneously at a dose of 3 IU/kg. Blood glucose level was monitored before the induction of diabetes and on day 0, 7, 14 after the establishment of diabetes mellitus using the glucose oxidase method [25].

2.2. Gastric histopathology, mucous content, parietal and mucous cell counts

Five (5) animals in each group of study group A were used for gastric mucous content analysis while the remaining 5 animals in the groups were used for mucous cell count, parietal cell count and histopathological evaluation. Gastric mucous content was estimated using the Alcian blue technique as described by Corne et al. [26]. Mucous cell count was estimated using the Periodic Acid Schiff (PAS) reaction technique while gastric histopathology and parietal cell count were estimated using hematoxylin and eosin staining techniques as described by Adewoye and Salami [22].

2.3. Biochemical analysis

Blood samples were obtained from the retro-orbital plexus of each rat in study group B after light anaesthesia into plain sample bottles. The blood samples were allowed to coagulate and then centrifuged at 3000*g* for 10 min at 4 °C to obtain serum. The serum samples were thereafter used for biochemical analysis. Stomach samples were also harvested from each animal, weighed and opened up by making an incision through the lesser curvature, weighed and homogenized on ice in 1.15% KCl buffer (pH = 7.4) [27]. The gastric homogenates was centrifuged at 10,000 rmp for 10 min at 4 °C. The supernatant obtained was used for biochemical assay. Serum and gastric homogenates were analyzed for superoxide dismutase (SOD) [28], lipid peroxidation [29] and nitric oxide (Griess reaction as described by Green et al. [30]) levels.

2.4. Statistical analysis

Results obtained are expressed as mean $\pm$ SEM. Statistical significance was taken at $P < 0.05$ using the Student's *T*-test. All analysis was carried out using the Microsoft excel 2007 statistical package.

3. Results

3.1. Body weight changes

Animals in control group had a relatively constant body weight throughout the experiment. Values obtained in this group show a 9.94% increase in body weight when compared with their initial values before diabetes induction. At day 14 diabetic untreated animals had a 6.25% reduction in body weight compared to their initial body weight while animals in the DMg250 and DI groups exhibited a 6.25% and 4.04% increase in body weight respectively compared to their body weights before diabetes induction (Table 1).

3.2. Blood glucose studies

Fasting blood glucose level remained relatively stable in the control group as values obtained were still within the physiological range. Diabetic untreated group (DU) exhibited a significant ($p < 0.05$) increase in blood glucose level after diabetes induction and the values obtained in this group remained consistently higher ($p < 0.05$) than values obtained in the control group throughout the duration of the experiment (Table 2). The diabetic treated groups also had significant increase ($p < 0.05$) in blood glucose level on induction of diabetes mellitus, however values obtained by day 14 indicates a 70.1% and 71.9% reduction in blood glucose level in the DMg250 and DI treatment groups respectively when compared with the DU group (Table 2).

3.3. Superoxide dismutase (SOD) studies

The values obtained show a reduction ($p < 0.05$) in serum SOD level of all diabetic animals compared to control (Table 3). Values obtained in the DMg250 treatment group were significantly reduced compared to DU while serum SOD values obtained in the DI group were comparable to that of the DU treatment group (Table 3). Gastric SOD level however was significantly increased ($p < 0.05$) in the control (0.63 ± 0.04 SOD units/ml),

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