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Comparative angioprotective effects of magnesium compounds

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ABSTRACT

Magnesium (Mg) deficiency is implicated in the development of numerous disorders of the cardiovascular system. Moreover, the data regarding the efficacy of different magnesium compounds in the correction of impaired functions due to low magnesium intake are often fragmentary and inconsistent. The aim of this study was to compare the effects of the most bioavailable Mg compounds (Mg L-aspartate, Mg N-acetyltaurate, Mg chloride, Mg sulphate and Mg oxybutyrate) on systemic inflammation and endothelial dysfunction in rats fed a low Mg diet for 74 days. A low Mg diet decreased the Mg concentration in the plasma and erythrocytes, which was accompanied by a reduced concentration of eNOs and increased levels of endothelin-1 level in the serum and impaired endothelium-dependent vasodilatation. These effects increased the concentration of proinflammatory molecules, such as VCAM-1, TNF-α, IL-6 and CRP, indicating the development of systemic inflammation and endothelial dysfunction. The increased total NO level, which estimated from the sum of the nitrate and nitrite concentrations in the serum, may also be considered to be a proinflammatory marker. Two weeks of Mg supplementation partially or fully normalised the ability of the vascular wall to effect adequate endothelium-dependent vasodilatation and reversed the levels of most endothelial dysfunction and inflammatory markers (except CRP) to the mean values of the control group. Mg sulphate had the smallest effect on the endothelin-1, TNF-α and VCAM-1 levels. Mg N-acetyltaurate was significantly more effective in restoring the level of eNOS compared to all other studied compounds, except for Mg oxybutyrate. Taken together, the present findings demonstrate that all Mg compounds equally alleviate endothelial dysfunction and inflammation caused by Mg deficiency. Mg sulphate tended to be the least effective compound.

Background and aims

Endothelial dysfunction underpinned by systemic inflammation is an important pathophysiological hallmark of atherosclerosis, arterial hypertension, diabetes mellitus and coronary heart disease [1,2].

Because magnesium (Mg) regulates the activity of more than 350 enzymes and serves as physiological blocker of N-methyl-D-aspartate receptors and Ca channels, it plays a key role in the modulation of the CNS and cardiovascular system function [3]. Mg deficiency is widely spread but unfortunately an underestimated and under-recognised disorder of elementary status [4] that can aggravate the course of cardiovascular disorders [5].

The role of Mg deficiency in the development of endothelial dysfunction was investigated in several preclinical and clinical studies. Mg restriction in the surrounding medium upregulates interleukin-1 (IL-1), vascular cell adhesion molecule-1 (VCAM) and plasminogen activator inhibitor (PAI)-1 [6,7]. Low Mg concentrations reversibly inhibit endothelial proliferation and severely

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impair the endothelial migratory response. Some transcripts that contribute to the adhesion of endothelial cells to substrates and their migration, such as proto-oncogene tyrosine-protein kinase Src, ezrin, CD9, cytohesin and zyxin, were modulated by exposing human umbilical vein endothelial cells (HUVECs) to low Mg-containing medium [6]. According to Paravicini et al., inherited hypomagnesaemia in mice is accompanied by an outward hypertrophic remodelling of the vascular wall, significantly elevated expression of the Mg transporter TRPM7 and reduced expression of the anti-inflammatory molecule annexin-1 [7].

In cultured human endothelial cells, low Mg promotes endothelial senescence, which contributes to the development of atherosclerosis [8].

Song et al. found that Mg intake in healthy women is inversely associated with the plasma concentrations of CRP (c-reactive protein), E-selectin, IL-6 and sICAM-1 (soluble Intercellular Adhesion Molecule 1) [9]. Another study conducted by Brown et al. provided evidence that dietary Mg supplementation restored the impaired vasoactive responses in isolated rat aorta induced by chronic ethanol consumption [10].

The data on the efficacy of different Mg compounds in correcting impaired functions due to low Mg intake are often incomplete and inconsistent. Barbagallo et al. evaluated the effects of Mg pidolate oral supplementation on endothelial function in elderly diabetic and hypertensive subjects. Mg administration resulted in increased Mg-ion concentration, which significantly improved the postischaemic endothelial-dependent flow-mediated dilatation [11]. The work of Heidarianpour et al. focused on the effects of chronic Mg sulphate administration on the improvement of the endothelium-dependent and endothelium-independent dilatation as well as identifying the probable mechanism associated with this effect in the skin microvasculature of diabetic rats. They concluded that the Mg compound could improve the skin microvasculature of diabetic rats by potentiating the nitric oxide pathway [12].

Benefit of Mg repletion in patients suffering from cardiovascular diseases is evident [13], and some Mg-containing agents have been recommended for Mg repletion in patients with cardiovascular diseases: Magnosolv-Granulat (Mg carbonate and Mg oxide), magnerot (Mg orotate), Asparkam-L (K,Mg L-aspartate) and Panangin (K,Mg aspartate). However, the bioavailability of some of these compounds has been shown to be lower than that of Mg chloride and some organic Mg compounds, such as Mg L-aspartate, Mg oxybutirate and Mg N-acetyltaurate [14,15]. This fact suggests that the compounds could provide biological effects of different intensities.

The aim of this study was to compare the effects of the most bioavailable Mg compounds on the systemic inflammation and endothelial dysfunction caused by Mg deficiency.

Materials and methods

Animals and experimental model

The experiments were carried out on 56 adult male Wistar rats initially weighing 225 ± 25 g and obtained from the nursery of the Hygiene and Plant Pathology Institute (Volgograd, Russia). They were group-housed (up to 5 animals per cage) side-by-side in a temperature- (22–24 °C) and humidity-controlled (50–60%) environment under a 12 h light/dark cycle (lights on at 07:00 h) and provided with food (experimental diet) and water ad libitum. All experimental procedures were designed to minimise animal suffering as well as the number of animals used and were approved by the national ethical committee on animal care and use in compliance with international laws and policies (Regional Independent Ethical Committee on Animal Care and Use, Research Centre of Russian Academy of Medical Sciences and Administration of Volgograd Region, Protocol 93-2009, 14.03.2009).

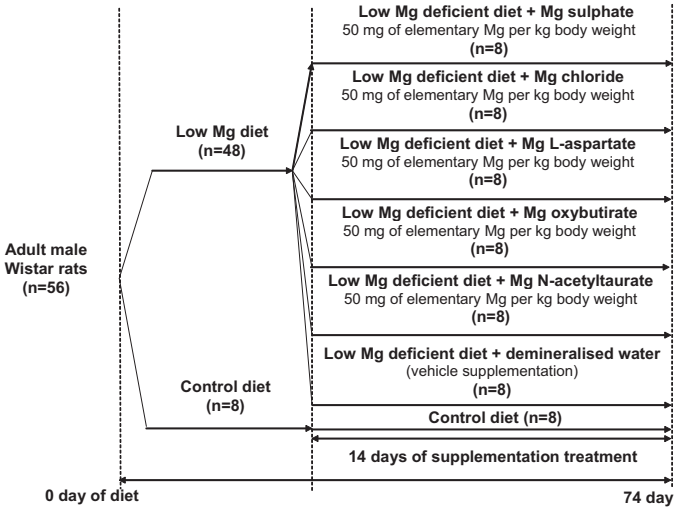

Fig. 1. Design of experiment.

Diet

To induce hypomagnesaemia, the rats were initially divided into two groups (Fig. 1). As described previously [16], the first group received a low Mg diet (Mg content ≤15 mg/kg) and demineralised water for 2 months (Fig. 1). The other group was fed a basal control diet (Mg content ≈500 mg/kg) and water (with Mg content 20 mg/L) for equal duration. The Mg-deficient diet contained (per kilogram of diet) 200 g of casein with a Mg content of ≤5 mg/kg (Open Company 'Mustang', Moscow, Russia), 3 g of DL-methionine (MP Biomedicals, USA), 50 g maize oil, 700 g of potato starch with a Mg content of ≤20 mg/kg (Joint Stock Company Argo, Russia), 35 g of a mineral mixture without Mg oxide, 10 g of AIN-93 vitamin mix (MP Biomedicals) and 2 g choline bitartrate (MP Biomedicals). The mineral mixture contained the following components per 1 kg of the diet: 500 g of dibasic calcium phosphate, 74 g of sodium chloride, 220 g of potassium citrate monohydrate, 52 g of potassium sulphate, 3.5 g of manganese carbonate (43–48% >Mn), 6 g of ferric citrate (16–17% Fe), 1.6 g of zinc carbonate (70% ZnO), 0.3 g of cupric carbonate (53–55% Cu), 0.01 g of potassium iodate, 0.01 g of sodium selenite, 0.55 g of chromium potassium sulphate and 142 g of finely powdered sucrose. The composition of the normal diet was the same but was supplemented with Mg oxide, which increased the Mg content to 500 mg per kilogram of food. The rats were fed their respective diets ad libitum.

Supplementations treatment

On the sixtieth day of being fed the Mg-deficient diet, the rats were treated with one of the following supplements.

- Mg sulphate (Joint Stock Company "Karpov chemical plant", Russia),
- Mg chloride (Reahimservis, LLC, Russia),
- Mg L-asparate (Joint Stock Company "Bioamid", Saratov, Russia),
- Mg oxybutyrate (Chemical Pharmaceutical Department, Research Institute of Pharmacology, Volgograd State Medical University, Volgograd, Russian Federation).
- Mg N-acetyltaurate (Chemical Pharmaceutical Department, Research Institute of Pharmacology, Volgograd State Medical University, Volgograd, Russian Federation).