RESEARCH ARTICLE

Investigating the effects of chronic magnesium oxide nanoparticles on aerobic exercise-induced antinociception in adult male rats

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Abstract

Background and Objective: Magnesium is a critical cation in human body that can block some receptors and channels associated with nociception. Aerobic exercise (AE) increases pain threshold in athletes. In this study, we investigated the effects of chronic administration of magnesium oxide nanoparticles (MgONPs) and MgO on nociception in the presence and absence of AE-induced analgesia. **Materials and Methods:** Adult male Wistar rats were divided into six groups: Two controls (saline and exercise groups), four intervention groups: MgONPs and bulk MgO groups (receiving intraperitoneal 1 mg/kg for 5 days/week and 6 weeks) with and without exercise. The exercise groups were trained 30 min using treadmill after the injections. At the end of the 6th week, analgesia time was evaluated by hot plate test. **Results:** AE significantly reduced pain response compared with the control group ($P < 0.01$). In addition, both MgO and MgONPs significantly reduced pain response than the control group ($P < 0.001$). There were no significant differences between analgesic effect of exercise alone and MgO or MgONPs with exercise. **Conclusion:** The analgesic effects of AE and MgO supplements are probably induced by common mechanisms in the central nervous system.

Key words: Aerobic exercise, magnesium oxide, nanoparticles, pain, rat

INTRODUCTION

Pain is a defensive and protective mechanism and one of the most unpleasant feelings in life; therefore, many efforts have been done to control and reduce it.[1] Magnesium (Mg) is an essential mineral and a cofactor for many enzymatic reactions involving in various processes including cell growth and proliferation, muscle contraction, and nerve activity.[2] It is shown that magnesium sulfate and magnesium chloride alone or in combination with pain-reducing drugs such as some opioid analgesics can significantly reduce the pain.[3] With developing nanotechnology in recent years, usage of nanomaterials is rapidly increased. Furthermore, metal oxide nanoparticles such as magnesium oxide nanoparticles (MgONPs) have been used in different cases including medical conditions and physiological responses.[4-6] An animal study showed that acute intake of MgONPs in mice-induced analgesic and anti-inflammatory effects in some pain tests.[6,7] On the other hand, exercise and physical activity can activate endogenous analgesic mechanisms through different pathways; therefore, pain threshold in athletes is higher compared with ordinary people.[8]

Body magnesium is consumed during physical activities which results in negative effects on energy metabolism and physical activity and some athletes use magnesium supplements for their optimal performance.[9,10] In line with

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our previous studies on MgONPs and pain perception in animal models,[6,7] this study was aimed to comparatively investigate the effects of chronic administration of MgONPs and MgO on nociception in the presence and absence of aerobic exercise-induced analgesia in adult male rats.

MATERIALS AND METHODS

A total of 60 adult male Wistar rats (weighing 185 ± 20 g) were used and housed in groups of 4 per cage and kept under standard laboratory conditions (temperature 22 ± 2°C, 12:12 h light:dark cycle). After 1 week, they were randomly divided into six homogenous groups (n = 10) and treated daily (5 days/week) for 6 weeks as follows: Saline control group, groups that received saline with exercise, groups that received MgO (Merk Co; Germany) and MgONPs (Lolitech Co; Germany, <100 nm) [Figure 1] (1 mg/kg, intraperitoneal injection) with and without exercise.

For injection of MgONPs and MgO, they were dispersed in saline 0.9%, by ultrasonic bath (S2600) for 15 min. All drugs injected at the dosage of 10 ml/kg. 30 min after injection, training groups allowed exercising.

Treadmill training began by familiarizing the rats with the apparatus for 4 days by placing them on the motorized-driven treadmill. The training group exercised 5 days/week for 6 consecutive weeks. The exercise period was divided into the three steps: Introductory stage: In the 1st week, rats exercised on a treadmill at a speed of 10 m/min. The angle of inclination was 0%, and a running time was 10–15 min/ day, overload stage: In the 2nd and 3rd weeks, the speed was increased to 12–28 m/min with a 0% gradient and the duration was increased to 15–60 min/day and maintains stage or stabilizes the work intensity: In 4th–6th weeks, the speed remained constant at 28 m/min, the angle of inclination was 0%, and the exercise duration was 60 min/day.[11,12]

According to the procedure of test, rats were placed on a hot plate maintained at 53 ± 0.5°C and the latency to lick the hind paw was recorded as pain index. A 45 s cutoff point was used to prevent tissue damage if no response occurred.[13] All tests took place in resting day for exercise groups without any injection.

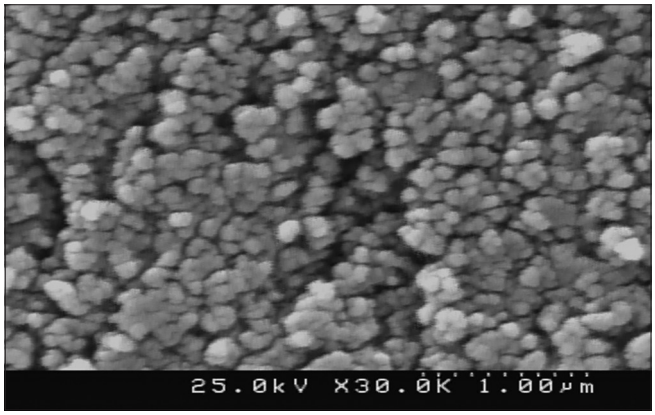

Figure 1: Scanning electron microscopic image of magnesium oxide nanoparticles powders

Data are presented as mean ± standard error of mean. Statistical differences were determined by ANOVA tests followed by the Student Newman Keuls *post hoc* test. Instate was used for data analysis. $P < 0.05$ was considered as significant level for all statistical analyses.

RESULTS

Effect of Exercise Activity, MgO, and MgONPs with and without Exercise on Nociception

The results show that exercise increased latency time compared with the group that just received saline indicating antinociception effect of exercise after 6 weeks [Figure 2a]. In addition, the MgO supplements increased latency time at the equal level in both groups in comparison with the control group ($P < 0.001$) indicating antinociception effect of MgO supplements [Figure 2b]. There are no significant differences between groups that doing exercise and receiving MgO/MgONPs compared to the exercise group alone or with each other [Figure 2c].

DISCUSSION

The results of this study showed a significant analgesic improvement in hot plate test following a 6-week period exercise [Figure 2]. The results demonstrated that this exercise period has analgesic effects in adult male rats.[8] Data showed a significant increase in latency time to heat stimulus in rats following MgO and MgONPs administration that support the findings of other similar studies.[7] It is possible that magnesium administration prevents the transmission of the pain message to higher centers through N-methyl-D-aspartate (NMDA) receptors' antagonist.[14,15] Magnesium is an antagonist of the NMDA receptor, and by blocking the receptor, magnesium prevents the entry of calcium to cell and consequent activation of the enzymes contributing in pain transmission process.[16] By blocking receptor channel and controlling its phosphorylation, magnesium controls message transmission as well as understanding of pain in the nervous system.[17] Results of this study imply magnesium role in mitigating pain. In addition to controlling NMDA receptors, the other possible analgesic mechanism of magnesium is affecting the purine receptors.[18,19] Pain activates the receptors and releases glutamate-inducing amino acids and initiates the process of pain generation and transmission.[18,19] Regarding the blocking property exhibited by magnesium in NMDA receptors as well as its controlling effect in porini receptors, the results of hot plate test would be justifiable. It seems that

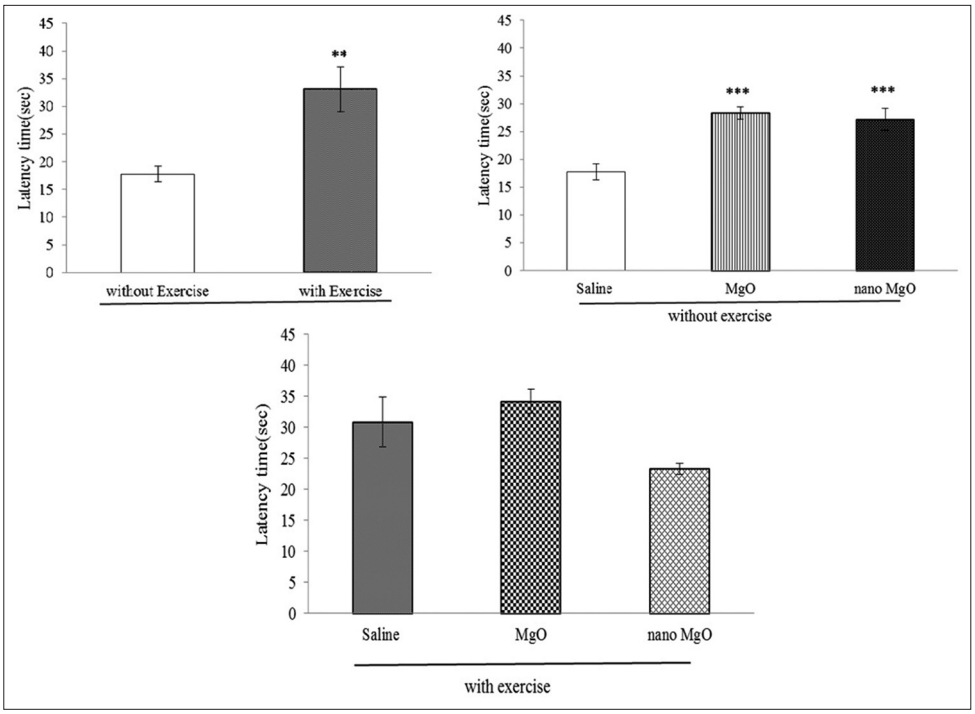

Figure 2: The comparisons of latency times between the different groups. Each bar shows mean ± standard error of mean. The ** and ***, respectively, denotes significant difference of $P < 0.01$ and $P < 0.001$ between the group and the respective control group

the pain mitigating effect of magnesium occurs to controlling the receptors and blocking NMDA receptors.

The results showed no significant difference between exercising groups and the groups that received MgO/MgONPs with exercising. Heavy exercises discharge magnesium through changing the blood magnesium level or through increased urination and sweat.[9] It seems that the amount of magnesium consumed in this study was substituted with the probable discharged on during exercising.

CONCLUSION

There was no difference between chronic usage of MgONPs and MgO on nociception and exercise activity could not change their efficacy. The benefit and harmful effects of chronic usage of MgONPs as a new source of magnesium in athletes need to more investigation.

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