HOW SIGNIFICANT IS MAGNESIUM IN THERMOREGULATION?

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ABSTRACT

Nine apparently healthy male subjects, mean age 22.8 yr, SD 4.1, free from disease, medication or addiction who gave informed consent, underwent acclimation process in a heat chamber; exposed during 2 h daily for 10 consecutive days to a temperature of 40°C and 40% relative humidity while walking on a treadmill elevated by 3° at a speed of 5 km/h (VO₂ 1.2 l/min⁻¹). Serum, mononuclear and erythrocyte magnesium (S-Mg, M-Mg and E-Mg, respectively) were monitored on day 1, 5 and 10 before and after the heat exposure. S-Mg decreased while M-Mg increased after the heat exposures, suggesting a shift of S-Mg to mononuclear cells. The decrease of S-Mg was sustained at the end of the acclimation process. E-Mg increased up to day 5 and decreased gradually approximating the baseline by day 10. Mg appears to play a significant role in heat acclimation.

KEY WORDS

serum, mononuclear, erythrocyte, magnesium, heat acclimation, thermoregulation

INTRODUCTION

Experimentally induced hyperthermia has been reported to cause lowering of extracellular Mg /1/. Bellar et al. /2/ found, following treadmill exercise during 1.5 h in a heat chamber under severe climatic conditions, an 8% decrease in S-Mg which could not be wholly explained by Mg loss in sweat. The decrease of Mg during heat
exposure is due not only to its loss through sweat, but also to magnesium diuresis /3/.

We studied eight unacclimated apparently healthy young males exposed during 2 h, on two consecutive days, in a heat chamber to a temperature of 40°C, and 50% relative humidity, while stepping up and down a 30 cm high bench at the rate of 12 steps/min /4/, and found a 12% decrease after the first exposure and a significant (p<0.01) decrease of 19% after the second. There was no change in any other laboratory variable.

In parallel, we have studied over a period of time, the effect of physical strenuous effort (40, 70 and 120 km forced marches) on Mg. We established that Mg deficiency occurs as a sequel of strenuous effort /5-7/. Our findings were confirmed by Deuster et al. /8/ and others, reviewed by, amongst others, Rayssiguier et al. /9/, and Stendig-Lindberg /10/.

In the latter studies we observed that the effect of strenuous effort on Mg was enhanced when the probands were exposed to high ambient temperature.

In order to evaluate the contribution of heat to the chronic Mg deficiency following effort, we conducted a preliminary study in the heat chamber using this time three exposures of 2 h each to a temperature of 40°C and 50% relative humidity, during low work load (~1.01 VO2 l-min\(^{-1}\)). After the third exposure, which took place five days after the second, we observed a 41%, highly significant decrease of S-Mg (p<0.001), which suggested that the effect of heat exposure on Mg was cumulative (Figs. 1-3).

In the present study we investigated the intracellular as well as the extracellular Mg during the heat acclimation process in order to observe the dynamics of Mg changes during heat exposure.

**MATERIAL AND METHODS**

**Selection of probands**

Nine apparently healthy male subjects, mean age 22.8 yr, SD 4.1 (see Table 1) gave informed consent to undergo 10 days of acclimation procedure. The probands were carefully selected to exclude the presence of history of past or concomitant serious disease, intercurrent infection, ongoing medication, alcohol or drug abuse and a cigarette.
TABLE 1

Anthropometric data of the probands (n=9)

<table>
<thead>
<tr>
<th></th>
<th>$\bar{x}$</th>
<th>SD</th>
<th>Range</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>22.8</td>
<td>4.1</td>
<td>19-25</td>
<td>21.5-24.1</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>172.6</td>
<td>7.8</td>
<td>162-185</td>
<td>166.6-178.5</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>69.6</td>
<td>9.5</td>
<td>56.7-87.3</td>
<td>62.3-77.1</td>
</tr>
</tbody>
</table>

Fig. 1: S-Mg before and after the first 2 h exposure to 40°C, 50% relative humidity in a heat chamber, day 1.
Fig. 2: S-Mg before and after the second 2 h exposure to 40°C, 50% relative humidity in a heat chamber day 2.

Fig. 3: S-Mg before and after the third 2 h exposure to 40°C, 50% relative humidity in a heat chamber day 6.
consumption exceeding 10 cigarettes a day. The extrapolated daily mean food Mg content of the probands was about 400 mg.

Experimental procedure

The acclimation procedure consisted of exposure to hot climate (40°C, 40% relative humidity) in a heat chamber, for 2 h daily for 10 consecutive days. During the exposure the probands walked on a treadmill elevated by 3° at a speed of 5 km/h (VO₂ max 1.2 l·min⁻¹). They were dressed only in shorts and sport shoes. Physiological parameters used consisted of continuous monitoring of the heart rate by ECG (UNIQ, CIS model 8799), recorded every minute (ELMA 1000), measurement of the rectal temperature (using YSI-409 thermistors), the skin temperature (YSI-401 thermistors), and measurement of fluid balance. The latter was calculated from the differences in the weight of the subjects before and after the exposure, corrected for urine loss and water intake.

Blood analysis

Blood was drawn using short stasis for the estimation of serum magnesium concentration (S-Mg), mononuclear magnesium content (M-Mg), and erythrocyte magnesium content (E-Mg), before and after the heat exposure on days 1, 5 and 10, using methods previously described /11, 12/.

Statistical analysis

Student’s dependent t-test and analysis of variance with repeated measures were used to analyze the data. All data are presented as mean ± SD. The 95% confidence intervals (CI) were calculated. Significance was accepted at p<0.05.

RESULTS

S-Mg

In spite of the careful selection of the probands which assured that only apparently healthy subjects were included, the baseline mean S-Mg was at the lower border of the national reference interval.
(estimated by subtracting only 1 SD from the mean, which is much closer to the reference range found at steady state, than the spurious value obtained after the conventional subtraction of 2 SD) /12/. This confirms earlier findings of a relatively high prevalence of Mg deficiency in the apparently healthy Israeli population /13/.

The mean S-Mg had decreased significantly at the end of the acclimation procedure compared to that at the beginning of the experiment (p=0.014, Student’s dependent t-test) and the analysis of variance with repeated measures showed a statistically significant difference between S-Mg before and after the heat exposures (P=0.019). The fluctuations of S-Mg, i.e. a decrease after each exposure with a rebound on its termination, were statistically significant on days 5 and 10 (P=0.005 and P=0.046, respectively) (see Fig. 4), and were opposite to those of M-Mg (Fig. 5).

M-Mg

The baseline mean M-Mg was significantly below the national mean found in the apparently healthy Israeli population /12/ (p<0.001, Student’s independent t-test).

The fluctuations of M-Mg content, i.e. the rise during the heat exposure and the subsequent fall, are shown in Fig. 5, and are opposite to those of S-Mg seen in Fig. 4. The baseline M-Mg value did not differ significantly from the end value on day 10, using Student’s dependent t-test, however, on analysis of variance with repeated measures, a trend towards a borderline significance (P=0.102) was observed on comparing the three M-Mg values before and after the heat exposures.

E-Mg

E-Mg showed an increase which peaked after the heat exposure on day 5, followed by a decrease which became statistically significant on day 10 (p=0.046, Student’s t-test). There was no statistically significant difference between the baseline E-Mg and the end value (Student’s dependent t-test), because although the E-Mg rose at first in response to the heat acclimation process, it subsequently decreased and at the end of the experiment approximated the baseline value (Fig. 6).
Fig. 4: S-Mg values during the acclimatization procedure. A = measurement after exposure on day 1, 5 and 10 (A₁, A₂, A₃, respectively). B = baseline value on day 1, 5 and 10 (B₁, B₂, B₃, respectively).

Statistically significant decreases of S-Mg:

<table>
<thead>
<tr>
<th>Value</th>
<th>$\bar{x}$</th>
<th>SD</th>
<th>n</th>
<th>Range</th>
<th>95% CI</th>
<th>Pairs compared</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>B₁</td>
<td>0.757</td>
<td>0.07</td>
<td>9</td>
<td>0.70-0.87</td>
<td>0.70-0.81</td>
<td>B₁; A₂</td>
<td>0.017</td>
</tr>
<tr>
<td>B₂</td>
<td>0.750</td>
<td>0.61</td>
<td>9</td>
<td>0.64-0.83</td>
<td>0.70-0.80</td>
<td>B₁; A₃</td>
<td>0.014</td>
</tr>
<tr>
<td>A₂</td>
<td>0.702</td>
<td>0.05</td>
<td>9</td>
<td>0.61-0.76</td>
<td>0.67-0.74</td>
<td>B₂; A₂</td>
<td>0.005</td>
</tr>
<tr>
<td>A₃</td>
<td>0.699</td>
<td>0.06</td>
<td>9</td>
<td>0.61-0.81</td>
<td>0.70-0.81</td>
<td>B₁; A₃</td>
<td>0.003</td>
</tr>
</tbody>
</table>

*Student’s dependent t-test

Other laboratory values

Hemoglobin, hematocrit, serum creatinine, total protein and albumen remained unchanged after the heat exposure.

Body weight

No significant change occurred in body weight during the acclimation process.
Acclimation

All probands showed the signs of acclimation (heart rate and rectal temperature reached a plateau after day 5).
DISCUSSION

The initial mean S-Mg and M-Mg were significantly lower than those found earlier on screening apparently healthy population samples /12,13/. Since the probands were carefully screened to exclude the possible presence of concomitant disease, medications or addiction, all of which could lower Mg, the decreased mean S-Mg and M-Mg point...
to a recent trend to an increased prevalence of Mg deficiency in the Israeli population.

The rise of the M-Mg content (Fig. 5) which occurred simultaneously with the decrease of S-Mg (Fig. 4) showed that a shift of Mg took place from the extracellular space to the mononuclear cells. An intracellular shift of Mg into erythrocytes was observed as well. This peaked on day 5 but was not sustained, since the E-Mg content decreased on day 10 (Fig. 6), i.e. at the end of the acclimation process.

Whether the purpose of this phenomenon is to increase tissue oxygenation, which is one of the many biological functions of Mg, or to aid in the energy processes which are magnesium dependent (oxidative phosphorylation, glucose metabolism and gluconeogenesis), this finding shows that Mg plays a significant role in the heat acclimation process.

The decrease of S-Mg after each exposure to heat was followed by a rebound on its termination (Fig. 4) which indicates an attempt to draw Mg from the body pools to replenish the loss from the extracellular compartment. This, however, was decreasingly successful with time (Fig. 4) and a growing deficit was demonstrated by the significantly decreased S-Mg at the termination of the acclimation process.

As shown in our preliminary studies (Figs. 1-3) the gradual downward trend of S-Mg values after heat exposures confirms that the latter have a cumulative effect leading over time to Mg deficiency.

We know from our previous studies of the effect of exertion on Mg /6,7/ that the deficiency of Mg found as a sequel to strenuous exercise in Israeli probands with daily food Mg intake of 200-300 mg /13/ persists over time. We assume, therefore, that the Mg deficiency found by us during the acclimation process will also persist beyond the 10 days of the duration of the experiment.

Although a part of the Mg deficit observed will be due to the exercise carried out during the acclimation process, its contribution, however, will be negligible because 1) the work load was low, 2) after exertion the change in E-Mg content would have remained sustained, whereas after repeated heat exposures there was a biphasic response (increase up to day 5 followed by a decrease).

It has been suggested that body temperature may be regulated by magnesium, by activating defenses against hyperthermia either via a central sedative effect on the hypothalamus or by a peripheral effect
achieved by reducing neuromuscular excitability /14/. In Mg deficit, these two antipyretic effects of Mg will fail. It was therefore proposed that Mg deficiency may constitute an important factor in the pathogenesis of malignant hyperthermia, e.g. heat stroke /3/, or exertional heat stroke /15,16/. This assumption is supported by the fact that the severe energy depletion which characterizes heat stroke /17-19/ is invariably found in profound Mg deficiency states as well, together with a number of other clinical manifestations characteristic of both conditions.

CONCLUSION

Our study shows that an intracellular shift of Mg takes place during heat exposure. This may serve to activate the defenses against hyperthermia and indicates that Mg plays a role in thermoregulation. However, the concomitant decrease of S-Mg culminating in a significant lowering at the end of the acclimation process signifies the presence of Mg deficiency. This is due not only to Mg loss via sweat and urine due to heat exposure /3/, but also to an increased demand for Mg caused among other things by increased energy metabolism - which is Mg dependent - in high ambient temperature.

We conclude, therefore, that unless there is an adequate supply of Mg to compensate for the increased demand, repeated heat exposures may over time lead to severe Mg deficiency and a failure of thermoregulation, e.g. heat stroke, exertional heat stroke, or other forms of malignant hyperthermia.

Further research is needed and should focus on studying 1) how to meet the increased requirement for Mg during heat exposure, and 2) the Mg status in malignant hyperthermia.

ACKNOWLEDGEMENT

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REFERENCES